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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Date: 02/03/2000

Subject: **PP#7F4856 and PP#6F4784; DICLOSULAM on PEANUTS and SOYBEANS.** Human Health Risk Assessment for New Reduced-Risk Insecticide.

DP Barcode:	D262935	PRAT Case:	288998
Submission No.:	S526363	Caswell No.:	None
Chemical No.:	129122	Class:	Herbicide
Trade Name:	Strongarm*	EPA Reg No.:	62719-EII
40 CFR:	Not Registered		
MRID No.:	None		

To: T. Colvin-Snyder/J. Tompkins, PM Team 25
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02/10/2000

The Health Effects Division (HED) has conducted a human health risk assessment for the new herbicide active ingredient, diclosulam, for the purpose of making a tolerance and registration eligibility decision to establish the uses (peanuts and soybeans) requested by the petitioner, Dow AgroSciences.

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1.0 EXECUTIVE SUMMARY

♦ **For a LIST of the ATTACHMENTS to this review, see Section 7.0.**

Diclosulam is a new active ingredient (ai) which currently has no registered food or non-food uses. This ai belongs to the triazolopyrimidine sulfonamide class of herbicides; this class of herbicides also includes the active ingredients cloransulam-methyl and flumetsulam. The subject petitions propose **the first food uses** for this ai. There are no Codex, Canadian or Mexican maximum residue limits established for diclosulam. Diclosulam is a reduced-risk chemical.

Dow AgroSciences, the petitioner, has submitted petitions for the establishment of permanent tolerances for residues of diclosulam (also referred to as XDE-564) in or on peanut and soybean. Diclosulam is a broad spectrum herbicide for control of broadleaf weeds. The petitioner is also requesting Section 3 registration for an end-use product Strongarm*, (EPA File Symbol 62719-EII) containing diclosulam as the sole active ingredient. The product is formulated as a water dispersible granular containing 84% diclosulam. Specifically, the petitions propose the establishment of tolerances for residues of diclosulam, N-(2,6-dichlorophenyl)-5-ethoxy-7-fluoro[1,2,4]triazolo[1,5-c]pyrimidine-2-sulfonamide, in or on the following commodities:

Soybean, seed	0.020 ppm
Peanut, nutmeat	0.020 ppm

For peanut, the product is proposed for one preplant incorporated, preplant surface, or preemergence application at 0.016-0.024 lb ai/A. The herbicide may also be applied at the peanut cracking through pegging stage when weeds are in the 1 to 4 leaf stage and actively growing as a broadcast spray at 0.008-0.016 lb ai/A; however, the maximum number of postemergent applications is not specified.

For soybean, the product allows a maximum of one preplant incorporated, preplant surface, or preemergence application at 0.024-0.032 lb ai/A/season.

The label prohibits application of diclosulam by aerial means or through any type of irrigation system, and to muck or peat soils. The label also prohibits the grazing of livestock and the harvest of forage and hay in treated areas. Preharvest intervals (PHIs) are not specified for either soybean or peanut. The proposed label needs to be revised to include PHIs for peanut and soybean and to clarify the rotational crop restrictions.

The submitted product chemistry data for diclosulam technical grade active ingredient (TGAI), XDE-564, were reviewed by Registration Division (Memo, 11/23/98, H. Podall, D249660). No additional data are required.

HED has evaluated (12/15/99) the residue chemistry data base, which is from residue field trials and processing studies. There are minor data gaps and a revised Section B (proposed label) is needed. With the exception of the analytical method validation by ACL/BEAD, the residue chemistry data gaps do not preclude the establishment of the requested tolerances. The HED

Metabolism Assessment Review Committee (MARC) has determined (12/6/99) that the residue of concern for risk assessment and tolerance setting purposes in primary crops is the parent compound, diclosulam. The MARC also determined that finite transfer of diclosulam residues to meat, milk, poultry, and eggs is not expected (40 CFR§180.6(a)(3) category). Additionally, the MARC has requested the analysis of drinking water (drinking water data to be requested by EFED), plant metabolism and/or crop field trial samples of peanut and soybean for residues of 2,6-dichloroaniline (2,6-DCA). The additional data concerning 2,6-DCA are considered confirmatory data. The petitioner has proposed Capillary Gas Chromatography/Mass Selective Detection Methods GRM 96.01 and GRM 94.19 and GRM 94.19.S1 for the enforcement of tolerances in peanut and soybean commodities. Method validation recoveries indicate that this method adequately recovers residues of diclosulam from peanut, soybean, and their processed commodities. The validated limit of quantitation for all matrices is 0.01 ppm. Adequate independent method validation data have been submitted for this method. These methods have been forwarded to ACL/BEAD for validation. The validation by ACL/BEAD should be completed prior to the establishment of the proposed tolerances.

The HED Hazard Identification Assessment Review Committee (HIARC) met on 10/26/99 to evaluate the toxicology data base, establish Reference Doses (RfDs), and select toxicological endpoints for dietary and occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to diclosulam, as required by the Food Quality Protection Act (FQPA) of 1996.

There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158. However, the Ames mutagenicity test has data gaps (highest dose tested not high enough) and both the acute neurotoxicity study (guideline) and the 1-year neurotoxicity study (non-guideline) are classified unacceptable pending the submission of additional information. Both neurotoxicity studies are not required for the proposed food use.

The scientific and regulatory quality of the toxicology data base is high and is considered sufficient to clearly define the toxicity of diclosulam. There is high confidence in the hazard and dose-response assessments conducted.

In general, the toxicology studies conducted on diclosulam demonstrate that it has few or no biologically significant toxic effects at relatively low-dose levels in many animal studies. Diclosulam generally has low acute toxicity (Toxicity Category IV) and is not a dermal sensitizer. The BF-564 (84.3% a.i.) appeared to be slightly more irritating to the skin and eye than XDE-564 (97.6% a.i.). No significant treatment-related effects were noted in 21-day dermal studies in rabbits. Based on oral feeding studies, the primary target organs are the liver and kidney. In a subchronic rat feeding study, the primary target organ is the liver including increased relative organ weight, hepatocellular hypertrophy, and slight multifocal necrosis. Decreased body weight and kidney lesions were also noted. Liver effects were also noted in a subchronic dog study and included increased relative liver weight, centrilobular hepatocellular changes, and hepatocellular necrosis accompanied by elevated ALP, AST, and ALT. Other effects were decreased body weight, decreased food consumption, and renal changes in addition to hematological and clinical chemistry effects that were considered secondary to the debilitated

condition of the animals. In a chronic toxicity/oncogenicity study in the rat, the kidney is identified as a target organ. Changes in clinical chemistry and urinalysis parameters (indicative of altered renal tubule function) included increased creatinine, decreased urine specific gravity, increased urine volume, and decreased urinary protein concentration; also, microscopic renal tubular pathology was noted. The kidney was also a target organ in a mouse carcinogenicity study. Among the observed kidney effects were reduced vacuolization in the tubular epithelium, lower absolute and relative kidney weights, and focal dilatation with hyperplasia of the epithelial lining in the cortical tubules. Diclosulam was classified as a "not likely human carcinogen" based on the lack of evidence of carcinogenicity in rats or mice fed diclosulam, and the lack of evidence of mutagenic activity. No evidence of neurotoxicity was observed, although neurotoxicity studies are considered inadequate. Diclosulam is not a developmental or reproductive toxicant and there was no evidence for increased susceptibility of rat or rabbit fetuses to *in utero* exposure or rat pups to *post-natal* exposure to diclosulam.

The HIARC did not identify an appropriate toxicological endpoint attributable to a single oral exposure. Therefore, **no acute RfD was selected** and an acute dietary risk assessment is not required.

The HIARC selected a **chronic RfD of 0.05 mg/kg/day** (the no observable adverse effect level (NOAEL) equals 5 mg/kg/day; Uncertainty Factor (UF) = 100) for use in assessing chronic dietary risk. This chronic RfD is based on the 2-year combined chronic feeding/carcinogenicity study in rats, in which the following effects were observed at the lowest observable adverse effect level (LOAEL) of 100 mg/kg/day in both sexes: statistically significant decreases in body weight gain, changes in renal tubule and kidney function parameters, and increased incidence of male kidney pelvic epithelium hyperplasia.

The HIARC did not select a toxicological endpoint for short- or intermediate-term dermal risk assessments. Therefore, these risk assessments are not required. In a 21-day repeated dose dermal toxicity study in rabbit, no systemic or dermal toxicity was observed at 1000 mg/kg/day, the highest dose tested (limit dose). The systemic and dermal NOAEL is the limit dose of 1000 mg/kg/day and LOAEL is unidentified. The proposed use pattern for diclosulam indicates there is no potential for long-term dermal exposure. Thus, the HIARC concluded that a long-term dermal exposure assessment is not required.

The HIARC selected a toxicological endpoint for short- and intermediate-term inhalation risk assessments. The HIARC recommended that a route-to-route extrapolation should be made using the rabbit oral developmental study with the maternal/developmental NOAEL of 10 mg/kg/day based on the dose-dependent increased abortions, and decreased maternal body weight gain, food consumption, and fecal output. A margin of exposure (MOE) of 100 or greater is adequate for occupational exposure risk assessments. The proposed use pattern for diclosulam indicates there is no potential for long-term inhalation exposure. Thus, the HIARC concluded that a long-term inhalation exposure assessment is not required.

In accordance with the 1996 Cancer Risk Assessment Guidelines, the HIARC classified diclosulam as a "**not likely human carcinogen**" based on the lack of evidence of carcinogenicity in mice or rats. Therefore, this risk assessment is not required.

The FQPA Safety Factor Committee (SFC) met on November 15, 1999 to evaluate the hazard and exposure data for diclosulam. The SFC recommended that the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996) be removed (i.e reduced to 1x) in assessing the risk posed by this chemical for the following reasons:

* The toxicology database is complete for the assessment of the effects following *in utero* and/or *postnatal* exposure to diclosulam.
* The toxicity data provided no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or *postnatal* exposure.
* A developmental neurotoxicity study has not been required by HIARC.
* The exposure assessment will not underestimate the potential dietary (food and water) exposures for infants and children resulting from the use of diclosulam (no residential exposure is expected).

The chronic RfD (0.05 mg/kg/day), divided by the 1x FQPA Safety Factor, yields the chronic Population Adjusted Dose (chronic PAD) of 0.05 mg/kg/day, which is used in assessing chronic dietary risk. The SFC determined that the chronic PAD is to apply to ALL population subgroups.

The only risk assessments conducted in this review are an occupation inhalation assessment and a chronic (non-cancer) aggregate (food + water; there are no residential uses) risk assessment.

HED used the Dietary Exposure Evaluation Model (DEEM™) software for conducting a Tier 1 chronic (non-cancer) dietary (food) exposure analysis. Tier 1 assumptions are tolerance level residues and 100% crop-treated.

The chronic DEEM™ analysis indicates the resulting dietary food exposures occupy **<1% of the Chronic PAD for all population subgroups** included in DEEM™.

The Environmental Fate and Effects Division (EFED) has evaluated the environmental fate data base for diclosulam and performed a Tier 1 drinking water assessment (11/10/99, R. Pisigan, Jr. & R. Parker). In soil, diclosulam is mobile (K_{OC} = 55 mL/g.o.c.) and moderately persistent (aerobic soil half-life = 54 days). Diclosulam is expected to be a ground and surface water contaminant. There are no known prospective ground water or surface water studies for diclosulam, so the estimated environmental concentrations (EECs) are based on the EFED Tier 1 screening models of ground water (SCI-GROW) and surface water (GENEEC).

The EECs provided by EFED for assessing chronic aggregate dietary risk are **0.035 ppb** (in ground water, based on SCI-GROW) and **1.28 ppb** (in surface water, based on GENEEC modeling, 56-day average). The back-calculated DWLOCs for assessing chronic aggregate dietary risk **range from 490 ppb** for the population subgroup with the highest food exposure (Non-nursing Infants) **to 1700 ppb** for the U.S. Population (total) and Males (13 to 19 years old).

Thus, HED concludes with reasonable certainty that residues of diclosulam in drinking water will **not** contribute significantly to chronic aggregate dietary risk and that the chronic aggregate dietary risk from diclosulam residues will not exceed HED's level of concern (100% of the chronic PAD). This risk assessment is considered conservative and very protective of human health.

Only an inhalation toxicity endpoint was chosen for assessment of non-dietary exposure to diclosulam. For handlers, daily inhalation exposures were compared to the NOAEL of 10 mg/kg/day from an oral developmental study in rabbits (endpoint: dose-dependent increased abortions, and decreased maternal body weight gain, food consumption, and fecal output) to determine the risk for short-term and intermediate-term inhalation exposures. An endpoint for long-term inhalation exposure was not selected. Results that do not reach a target MOE of 100 present risk concerns. Chronic and/or long-term exposures are not expected for handlers.

An occupational postapplication exposure assessment was not conducted. Following the HED Exposure Science Advisory Council Policy# 008 (March 11, 1999), a decision to not perform an assessment of postapplication exposure to pre-emergent herbicides is based on two key factors: (1) reentry to perform routine hand labor tasks is not required; and (2) reentry activities that may be necessary tend to result in relatively low levels of dermal exposure because contact with treated media is minimal or infrequent. Because diclosulam is used primarily as a pre-emergent, soil applied herbicide, both of these criteria are met. Further, the only non-dietary route of exposure for which a toxicity endpoint was identified is inhalation, and inhalation is not regarded as a significant route of exposure for postapplication activities, especially for a pre-emergent herbicide.

No chemical-specific handler exposure data were submitted in support of this Section 3 registration. It is HED policy to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure Draft Policy # 7, dated 1/28/99).

Exposure for handlers who mix and load diclosulam were assessed wearing long pants, long-sleeved shirt, shoes plus socks and gloves, and using the product in water-soluble packets (WSP). Also, exposure for handlers who mix and load liquid diclosulam were assessed with the same clothing to cover cases when WSP are premixed before loading into tanks. Handlers who apply diclosulam by groundboom sprayer were assessed in the above clothing (except for the gloves), and using open cab tractors. The MOEs for inhalation, under the above circumstances, range from 250,000 to 1.4 million for handlers. These MOEs are greater than the target (100) and do not exceed HED's level of concern.

The proposed label for diclosulam (i.e., Strongarm*) has a 12-hour restricted entry interval (REI). The technical material has a Toxicity Category III for Acute Dermal, with all other acute studies resulting in Toxicity Category IV. Per the Worker Protection Standard (WPS), a 12-hour restricted entry interval (REI) is required for chemicals classified under Toxicity Category III. Therefore, the REI of 12 hours appearing on the Strongarm label is in compliance with the WPS.

There are no registered residential uses for diclosulam. However, spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the groundboom application method employed for diclosulam. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling as specified in section V. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

Conclusion: HED concludes that the toxicological, product chemistry, and residue chemistry data bases, and the human health risk assessments, support the establishment of tolerances for residues of the herbicide diclosulam in or on:

Soybean, seed ..... 0.020 ppm
Peanut, nutmeat ..... 0.020 ppm

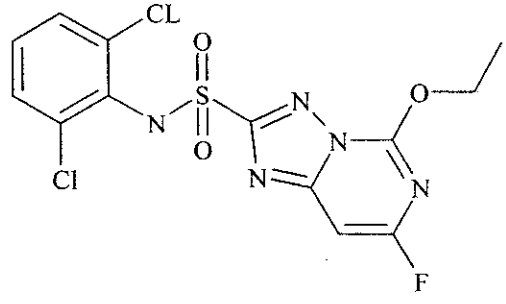
and the registration of Strongarm*; EPA File Symbol 62719-EII, for use on soybeans and peanuts. This conclusion is **contingent upon** receipt by the Agency of a suitably **revised Section B and adequate completion of the validation of the proposed analytical methods for enforcement by ACL/BEAD** (per Section 6.0 of this review). The revised Section B should include a PHI of 125 days for soybeans, a PHI of 30 days for peanuts, and should specify "small grains" as wheat, barley, oat, and rye. Registration of Strongarm* should be made conditional upon resolution of the stability of diclosulam residues under frozen storage in the poultry metabolism study and confined rotational crop study, receipt of confirmatory data for 2,6-DCA in peanut and soybean, and resolution of cited deficiencies of the toxicology database. The data deficiencies concerning the analytical method are discussed in detail in Section 6.0 and our review of 12/15/99 (Memo, L. Cheng, D249626).

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

♦ Reference: See Attachments 6 & 7.

Chemical Name:	N-(2,6-dichlorophenyl)-5-ethoxy-7-fluoro[1,2,4]triazolo[1,5-c]pyrimidine-2-sulfonamide (CAS nomenclature)
Chemical Group:	Triazolopyrimidine sulfonamide
Chemical Type:	Herbicide (broadleaf)
CAS Registry No.:	147150-21-9
Common Name:	Diclosulam (ANSI approved)
Other Names:	XDE-564
Trade Names:	Strongarm*
PC Code Number:	129122
Mode of Action:	Not reported.
Empirical Formula:	$C_{13}H_{10}Cl_2FN_5O_3S$
Molecular Weight:	406
Appearance:	Off-white powder
Melting Point:	218 - 221° C
Vapor Pressure:	N/A (solid at room temperature)
Partition Coefficient:	log P_{OW} = 0.85 (n-octanol/water, at pH 7)
	K_{OC} = 55 (soil/water)
Solubility in Water:	6 ppm (at 25° C)
Hydrolysis:	Stable (pH 7)
Half-Life:	119 days (photolysis)
	54 days (aerobic soil metabolism)
	107 days (aerobic aquatic metabolism)
Toxic Impurities:	None

Chemical Structure:



Diclosulam

3.0 HAZARD CHARACTERIZATION

A summary of the toxicological data base for diclosulam has been prepared as a separate document. This document is included as Attachment 2.

3.1 Hazard Profile

Diclosulam is a new chemical proposed for use as a broadleaf herbicide on peanuts and soybeans at this time. No residential uses have been requested. It is presumed, however, that additional food and/or non-food uses will be proposed in the future. Diclosulam belongs to the triazolopyrimidine sulfonamide class of herbicides; this class of herbicides also includes the active ingredients cloransulam-methyl and flumetsulam.

In general, the toxicology studies conducted on diclosulam demonstrate that it has few or no biologically significant toxic effects at relatively low dose levels in many animal studies. Diclosulam generally has low acute toxicity (Toxicity Category IV) and is not a dermal sensitizer. No significant treatment-related effects were noted in 21-day dermal studies in rabbits. In subchronic feeding studies with rats and dogs, the primary target organ is the liver. In the chronic feeding studies with rats and mice, the primary target organ was the kidney. Diclosulam was classified as a "not likely human carcinogen". No evidence of neurotoxicty was observed although neurotoxicity studies are considered inadequate. Diclosulam is not a developmental or reproductive toxicant and there was no evidence for increased susceptibility of rat or rabbit fetuses to *in utero* exposure or rat pups to *post-natal* exposure to diclosulam.

Toxicological endpoints for chronic dietary exposure and short- and intermediate-term inhalation exposure were identified for diclosulam. The HIARC selected a **chronic RfD of 0.05 mg/kg/day**. This chronic RfD is based on the 2-year combined chronic feeding/carcinogenicity study in rats. The NOAEL from this study was 5 mg/kg/day (with an uncertainty factor of 100). The effects observed at the LOAEL of 100 mg/kg/day in both sexes were: statistically significant decreases in body weight gain and kidney effects. For inhalation exposure assessment, the HIARC recommended that a route-to-route extrapolation should be made using the rabbit oral developmental study with the maternal/developmental NOAEL of 10 mg/kg/day based on dose-dependent increased abortions, and decreased maternal body weight gain, decreased food consumption, and decreased fecal output. A margin of exposure (MOE) of 100 or greater is adequate for occupational exposure assessments. The proposed use pattern for diclosulam indicates there is no potential for long-term inhalation exposure. Thus, the HIARC concluded that a long-term inhalation exposure assessment is not required.

3.2 FQPA Considerations

The FQPA Safety Factor Committee (SFC) met on November 15, 1999 to evaluate the hazard and exposure data for diclosulam. The SFC recommended that the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996) be removed (i.e reduced to 1x) in assessing the risk posed by this chemical for the following reasons:

* The toxicology database is complete for the assessment of the effects following *in utero* and/or *postnatal* exposure to diclosulam.
* The toxicity data provided no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or *postnatal* exposure.
* A developmental neurotoxicity study has not been required by HIARC.
* The exposure assessment will not underestimate the potential dietary (food and water) exposures for infants and children resulting from the use of diclosulam (no residential exposure is expected).

Detailed information concerning the conclusions of the meeting are included in the Report of the FQPA SFC for diclosulam which is included as Attachment 4.

3.3 Dose Response Assessment

The doses and toxicological endpoints selected for various exposure scenarios are summarized in **Table 1**.

Table 1. Summary of Toxicological Endpoints for Use in Human Risk Assessment			
EXPOSURE SCENARIO	**DOSE (mg/kg/day)**	**ENDPOINT**	**STUDY**
Acute Dietary	None	**This risk assessment is not required.** There is no appropriate study with a single dose and end-point for this risk assessment.	None
	UF = N/A	**Acute RfD = Not Applicable**	
Chronic Dietary (Non-cancer) **ALL Population Subgroups**	NOAEL = 5	Decreased body weight gain, changes in renal tubule and kidney function parameters, and increased incidence of male kidney pelvic epithelium hyperplasia. **This risk assessment is required.**	Chronic Toxicity/ Oncogenicity-Rat
	UF =100 FQPA = 1x	**Chronic RfD = 0.05 mg/kg/day** **Chronic Population Adjusted Dose (cPAD) = 0.05 mg/kg/day** **[This cPAD applies to ALL population subgroups.]**	
Short- and Intermediate-Term (Dermal)	NOAEL ≥1000	**This risk assessment is not required.** In a 21-day rabbit dermal toxicity study, no systemic toxicity was observed at the limit dose (1000 mg/kg/day).	21-Day dermal toxicity study (rabbit)
Long-Term (Dermal)	None	**This risk assessment is not required.** Based on the use pattern (1 application/year), there is no potential long-term dermal exposure/risk.	None
Short- and Intermediate-Term (Inhalation)	NOAEL= 10	Increased abortions and decreased maternal body weight gain, food consumption, and fecal output. **This risk assessment is required.**	Developmental Toxicity-Rabbit
Long Term (Inhalation)	None	**This risk assessment is not required.** Based on the use pattern (1 application/year), there is no potential long-term inhalation exposure/risk.	None
Cancer	None	In accordance with the 1996 Cancer Risk Assessment Guidelines, the HIARC classified diclosulam as a "**not likely human carcinogen**" based on the lack of evidence of carcinogenicity in mice or rats. **This risk assessment is not required.**	None

4.0 EXPOSURE ASSESSMENT

♦ References: See Attachments 5, 6, 8, 9, and 10.

4.1 Summary of Registered and Proposed Uses

Registered Uses. Diclosulam has no currently registered uses. Uses are currently proposed on peanut (PP#7F4856) and soybean (PP#6F4784). There are no residential uses and none are currently proposed.

Formulation. The formulation proposed for use on peanut and soybean for control of broadleaf weeds is Strongarm* 84% DF herbicide (EPA File Symbol No. 62719-EII), a water-dispersible granular formulation containing 84% by weight of diclosulam as the sole active ingredient.

Proposed Uses. For peanut, the product is proposed for one preplant incorporated, preplant surface, or preemergence application at 0.016-0.024 lb ai/A; the herbicide should be incorporated into the top 1 to 3 inches of the seedbed within 2 weeks of planting (preplant), or applied within 2 days after planting (preemergent). The herbicide may also be applied at the peanut cracking through pegging stage when weeds are in the 1 to 4 leaf stage and actively growing as a broadcast spray at 0.008-0.016 lb ai/A; however, the maximum number of postemergent applications is not specified.

For soybean, the product allows a maximum of one preplant incorporated, preplant surface, or preemergence application at 0.024-0.032 lb ai/A/season.

The label indicates that applications may be made with ground equipment using a sufficient spray volume (≥10 gal of water/A recommended) to provide uniform coverage. For postemergence applications, either a crop oil concentrate at 1.25% v/v or a non-ionic surfactant at 0.25% v/v must be included in the spray mixture. The label prohibits application of diclosulam by aerial means or through any type of irrigation system, and to muck or peat soils. The label also prohibits the grazing of livestock and the harvest of forage and hay in treated areas. Preharvest intervals (PHIs) are not specified for either soybean or peanut. **The proposed label needs to be revised to include PHIs for peanut and soybean. Based upon the submitted crop field trial data (see summary of field trial data below), a PHI of 125 days is appropriate for soybeans and a PHI of 30 days is appropriate for peanuts.**

The petitioner has proposed the following plantback restrictions for rotated crops: 4 months for small grains, 9 months for cotton, soybeans, and peanuts; 18 months for corn, rice, tobacco, and sorghum; and 30 months for all other crops due to phytotoxicity. HED has no objections to these proposed plantback restrictions. The rotational crop restrictions included on the submitted label are not adequate. **A revised Section B is required which specifies "small grains" as wheat, barley, oat, and rye.**

4.2 Dietary Exposure

A very brief summary of information from the residue chemistry review (Attachment 8) is given below. Minor data gaps in the residue chemistry data base include method validation in an Agency laboratory, frozen storage intervals and revised Section B (see Section 6.0 of this review).

Metabolism in Plants. Data depicting the metabolism of ^{14}C-diclosulam in peanut and soybean were submitted. Based on the results of the peanut and soybean metabolism studies, diclosulam undergoes extensive degradation. Diclosulam was not detected in soybean forage and mature bean. Two metabolites were identified in soybean forage: 7S-[3-aminosulfonyl-5-methoxy[1,2,4]triazolo[1,5-c]pyrimidinyl]cysteine (methyl-ASTP-Cys), a significant metabolite, and 7S-[3-aminosulfonyl-5-ethoxy-[1,2,4]triazolo[1,5-c]pyrimidinyl]cysteine (ASTP-Cys), a minor metabolite. In peanut, the activity levels were much higher in the triazolopyrimidine labeled samples than in the aniline labeled samples. The observation suggested that soil degradates containing the triazolopyrimidine ring system were preferentially taken up by the peanut plants compared to those containing only the aniline portion of the parent molecule. Results showed multiple components at <0.01 ppm and diclosulam was not detected in peanut forage and mature nut. The qualitative nature of diclosulam residues in plants is adequately understood for the purposes of this petition. The results of the peanut and soybean metabolism studies have been presented to the HED Metabolism Assessment Review Committee (Memo, MARC, 12/6/99, L. Cheng, D262014). The MARC has determined that the residue of concern for dietary exposure and tolerance setting purposes in primary crops is the parent compound, diclosulam. However, since diclosulam contains a 2,6-dichloroaniline (2,6-DCA) group, the petitioner also needs to provide levels of 2,6-DCA at the parts per billion range in primary crops for dietary risk assessment. Specifically, the MARC has requested the analysis of drinking water (drinking water data to be requested by EFED), plant metabolism and/or crop field trial samples of peanut and soybean for residues of 2,6-dichloroaniline (2,6-DCA). The additional data concerning 2,6-DCA are considered confirmatory data.

Metabolism in Rotational Crops. A study depicting the metabolism of [^{14}C]diclosulam in rotational crops was submitted and reviewed. The confined rotational crop study demonstrated that diclosulam does not accumulate in rotational crop commodities at >0.01 ppm at a 120-day plantback interval. The confined rotational crop study is adequate provided the petitioner furnishes information on the intervals for which samples and sample extracts were held in frozen storage prior to completion of laboratory analyses. If samples were stored longer than six months from harvest to definitive sample analysis, data demonstrating the storage stability of ^{14}C-residues in rotational crop matrices should accompany the submitted sample storage history. Following a soil application of [aniline-^{14}C] or [triazolopyrimidine-7,9-^{14}C]diclosulam at 0.050 lb ai/A (1.25x the maximum seasonal rate), radioactive residues were low (<0.05 ppm) in wheat and potato RAC samples from the 120-day plantback interval (PBI), with the exception of [triazolopyrimidine-7,9-^{14}C]-treated wheat straw (0.070 ppm). ^{14}C-Residues in wheat and potato

RACs resulting from the application of [aniline-^{14}C]diclosulam were lower (<0.003-0.007 ppm) than ^{14}C-residues resulting from the application of [triazolopyrimidine-7,9-^{14}C]diclosulam (0.008-0.070 ppm). For crops harvested from the [triazolopyrimidine-7,9-^{14}C]treated 120-day PBI plots, ^{14}C-residues were 0.008 ppm in potato tubers and 0.020, 0.025, and 0.070 ppm in wheat forage, grain, and straw, respectively. Lettuce crops planted at 120-, 161-, and 225-day PBIs failed due to phytotoxicity; Swiss chard planted at a 225-day PBI had ^{14}C-residues of 0.012-0.024 ppm but was stunted due to phytotoxicity.

Wheat and potato RAC samples containing radioactivity approaching or exceeding 0.01 ppm were adequately characterized by solvent extraction and HPLC analyses. No parent compound was detected. Minor unknown peaks (each at ≤0.009 ppm) were detected in aqueous and organic fractions of wheat forage and straw, along with a polar peak (R_t=3.0 min) from the wheat grain aqueous fraction containing 0.01 ppm. Further characterization efforts were made on post-extraction solids of wheat grain and straw (each ≤43.3%TRR, <0.02 ppm) indicating that ^{14}C-residues were incorporated as natural components (starch, lignin, and cellulose). Although characterization of ^{14}C-residues in a representative leafy vegetable was not achieved and no attempt was made to obtain samples of a leafy vegetable at PBIs longer than 225 days, no additional data on ^{14}C-residues in a rotated leafy vegetable are required for purposes of this petition as residues of diclosulam are unlikely to occur at detectable levels in rotational crops. The MARC has determined that limited field trials and tolerances for rotational crops are not required as long as the label specifies PBIs of 120 days (Memo, MARC, 12/6/99, L. Cheng, D262014).

Metabolism in Animals. Data depicting the metabolism of ^{14}C-diclosulam in lactating goats and laying hens were submitted. Based on the results of the goat and hen metabolism studies, diclosulam is metabolized primarily by dealkyklation of the ethoxy group and hydrolysis of the sulfonamide linkage.

The qualitative nature of the residue in animals is adequately understood based on acceptable studies conducted on goats and laying hens. The results of the goat and poultry metabolism studies have been presented to the HED Metabolism Assessment Review Committee. The MARC has determined (Memo, MARC, 12/6/99, L. Cheng, D262014) that finite transfer of diclosulam residues to meat, milk, poultry and eggs is not expected (40 CFR§180.6(a)(3) category). The Committee concluded that should feeding studies be necessary in the future, diclosulam should be determined. Furthermore, for dietary exposure assessment in ruminant liver, the level of diclosulam will be doubled to account for 5-hydroxy (5-desethyl) diclosulam.

In the goat, residues in the milk were very low and data show no bioaccumulation. Only the kidney and liver contained high enough activity for metabolite characterization. In liver, diclosulam accounted for 19% total radioactive residue or TRR (0.014 ppm) from the aniline label and 17.9% TRR (0.008 ppm) from the triazolopyrimidine label, and its 5-hydroxy metabolite accounted for 18.2% TRR (0.014 ppm) from the aniline label and 13.1% TRR (0.007 ppm) from the triazolopyrimidine label. In kidney, diclosulam was the major residue

identified at 48% TRR (0.052 ppm) from the aniline label and 37.6% TRR (0.058 ppm) from the triazolopyrimidine label. Also determined was a minor metabolite ASTP (4.6% TRR, 0.007 ppm) in kidney from the triazolopyrimidine label.

In poultry, concentrations of diclosulam were high in skin (0.224-0.225 ppm) and liver (0.179-0.193 ppm), and low in fat (0.011-0.014 ppm) and muscle (0.026-0.035 ppm). The highest concentrations in eggs, ~0.023 ppm, were observed on Day-5 for eggs from both aniline and triazolopyrimidine labels. Overall, >73% of the TRR in tissues and 50-60% in eggs was adequately identified or characterized. Parent diclosulam was the principle component of the residue, accounting for 23-27% of the TRR (0.042-0.053 ppm) in liver; 50-66% of the TRR (0.017 ppm) in muscle; 79-88% of the TRR (0.178-0.199 ppm) in skin; 62-94% of the TRR (0.006-0.013 ppm) in fat, and 35-37% of the TRR (0.008 ppm) in eggs. The sulfonamide bridge cleavage product, ASTP, accounted for 8.3-17.6% (0.002-0.023 ppm) in liver, muscle, and eggs from the triazolopyrimidine label. Trace amounts of a putative hydroxy phenyl diclosulam metabolite were also found in all hen matrices at ≤3% of the TRR (≤0.007 ppm).

Enforcement Method for Peanut and Soybean Commodities. The petitioner has proposed Capillary Gas Chromatography/Mass Selective Detection Methods GRM 96.01 (MRID No. 443151-03) and GRM 94.19 (MRID No. 44103507) and GRM 94.19.S1 (MRID No. 44103510) for the enforcement of tolerances in peanut and soybean. Method validation recoveries indicate that these methods adequately recover residues of diclosulam from peanut, soybean, and their processed commodities. The validated limit of quantitation (LOQ) is 0.01 ppm for all commodities and the limit of detection (LOD) was estimated to be 0.003 ppm for all matrices. Adequate independent method validation data have been submitted for this method. These methods have been forwarded to ACL/BEAD for petition method validation (Memo, 7/29/99, L. Cheng, D257959).

Multiresidue Methods Testing. The petitioner submitted data concerning the recovery of residues of diclosulam using FDA multiresidue method protocols (PAM Vol. I). Diclosulam was recovered through Protocol C. Protocol C is the GC screen procedure and is not adequate for enforcement purposes. The compound was not recovered from Protocol D, E, F due to its lack of mobility on the Florisil column, and in the case of Protocol D, the lack of sensitivity of the detector to diclosulam. Protocol A and B are not applicable to diclosulam. These data have been forwarded to FDA for evaluation. HED concludes the FDA multiresidue method protocols are not adequate for enforcement of the proposed tolerances.

Freezer Storage Stability Data. The submitted storage stability study on diclosulam is adequate and indicates that residues of diclosulam *per se* are stable at ~-20°C in soybean seed, forage, and hay for up to 1 year. The storage intervals and conditions of the residue and processing studies are adequately supported by the storage intervals depicted in the available storage stability study.

The maximum storage intervals (from harvest to residue analysis) of samples from the field and processing studies were as follows: peanut (39 days), soybean (8 months), and soybean meal, soybean hulls, and soybean crude/refined oil (1 month).

Magnitude of the Residue in Soybean. The submitted soybean field trial data are adequate. Geographic representation of tests on soybeans conformed to OPPTS Series 860 guidelines, and an adequate number of samples was analyzed. Tests were conducted in Region 2 (3 tests), Region 4 (6 tests) and Region 5 (15 tests) for a total of 24 tests. Residues of diclosulam were below both the LOQ (<0.01 ppm) and the LOD (<0.003 ppm) in/on all soybean seed samples (n=81) harvested 125-158 days after a single preplant incorporated or preemergence application of diclosulam (83.4 or 84.2% DF) at 0.031-0.047 lb ai/A (1-1.5x the proposed maximum seasonal rate). Residues were also below the LOQ and LOD (<0.003 ppm) in/on three samples each of soybean forage and hay harvested 83-102 days after a single preplant incorporated treatment at 0.038-0.047 lb ai/A (1-1.5x).

The available residue data support the proposed tolerance at 0.020 ppm for residues of diclosulam in/on soybean seed. Residues were nondetectable (<0.003 ppm) in/on all 81 samples of soybeans treated at 1-1.5x. Diclosulam residues were also nondetectable (<0.003 ppm) in/on seed harvested from applications at exaggerated rates (~3 and 8x). The proposed label includes a restriction against grazing treated areas or harvesting forage and hay from treated areas; therefore, tolerances for residues in/on soybean forage and hay are not required at this time.

The proposed label does not specify a PHI. Based on the available data a 125-day PHI is appropriate and should be added to the proposed label.

Magnitude of the Residue in Peanut. The submitted peanut field trial data are adequate. Geographic representation of tests on peanuts conformed to OPPTS Series 860 guidelines and an adequate number of samples was analyzed. Field trials were conducted in Region 2 (14 tests), Region 3 (2 tests), Region 6 (4 tests), and Region 8 (2 tests) for a total of 22 tests. Residues of diclosulam were <0.003 ppm (<LOD) and <0.006-0.765 ppm in/on 22 samples each of peanut nutmeat and hay harvested 16-32 days after a split application of diclosulam (84.2% DF) consisting of a preplant incorporated or preemergence treatment at 0.031 lb ai/A followed 81-144 days later by a postemergence treatment at 0.024 lb ai/A, for a total of 0.055 lb ai/A (1.4x the proposed maximum seasonal rate).

The proposed label does not specify a PHI. Based on the available data a 30-day PHI is appropriate and should be added to the proposed label.

The available residue data support the proposed tolerance at 0.020 ppm for residues of diclosulam in/on peanut nutmeats. Residues were nondetectable (<0.003 ppm) in/on all 22 samples of nutmeats treated at 1.4x. Diclosulam residues were also nondetectable (<0.003 ppm) in/on seed harvested from applications at exaggerated rates (~3 and 8x). The proposed label includes a restriction against grazing treated areas or harvesting forage and hay from treated

areas. No tolerance for residues in/on peanut hay is needed since the proposed label includes a restriction against grazing treated areas or harvesting forage and hay from treated areas.

Magnitude of the Residue in Soybean Processed Commodities. The submitted soybean processing data are adequate for the purposes of this petition. The processing data indicate that residues of diclosulam do not concentrate in soybean processed commodities. Residues of diclosulam were <0.003 ppm (<LOD) in/on two soybean seed samples harvested 99-127 days after a single at planting preemergence application of diclosulam at 0.09 or 0.25 lb ai/A (~3x or ~8x the proposed rate). Residues were <0.003 ppm (<LOD) in each of two meal, hull, refined oil samples processed from the treated soybean RAC samples. No tolerances for residues of diclosulam in soybean processed commodities are required.

Magnitude of the Residue in Peanut Processed Commodities. The submitted peanut study is adequate. Residues of diclosulam were below both the LOQ (<0.01 ppm) and LOD (<0.003 ppm) in/on four nutmeat samples harvested ~30 days after split pre- and postemergence applications of diclosulam (84.2% DF) totaling of 0.17 lb ai/A (4.3x the proposed maximum seasonal rate). Peanut processed fractions were not generated. As all peanut nutmeat samples from the RAC field trials and exaggerated rate trials showed residues of diclosulam <0.003 ppm (<LOD), no tolerances for residues of diclosulam in peanut processed commodities are required. The maximum theoretical concentration factor for peanut is 3x.

International Harmonization. There are no established or proposed Codex, Canadian or Mexican limits for residues of diclosulam in/on plant or animal commodities. Therefore, no compatibility issues exist with regard to the proposed U.S. tolerances discussed in this petition review.

4.2.1 Food Exposure

4.2.1.1 Acute Dietary (Food) Exposure

The HIARC did not identify an appropriate toxicological endpoint attributable to a single (acute) dietary exposure. **This risk assessment is not required.**

4.2.1.2 Chronic (Non-Cancer) Dietary (Food) Exposure

HED used Dietary Exposure Evaluation Model (DEEM™) software for conducting a chronic dietary (food) risk analysis (Attachment 5). DEEM™ is a dietary exposure analysis system developed by Novigen Sciences, Inc. that is used to estimate exposure to a pesticide chemical in foods comprising the diets of the US population, including population subgroups. DEEM™ contains food consumption data as reported by respondents in the USDA Continuing Surveys of Food Intake by Individuals conducted in 1989-1992.

Chronic RfD = 0.05 mg/kg/day; Chronic Populated-Adjusted Dose (Chronic PAD) = 0.05 mg/kg/day; Apply the Chronic PAD to All Population Subgroups. A Tier 1 chronic dietary risk assessment was conducted via DEEM™. The assumptions of this Tier 1 analysis were tolerance level residues and 100 percent crop-treated. The following tolerance levels were used in the analysis:

Peanut, nutmeat ..... 0.020 ppm
Soybean, seed ..... 0.020 ppm

Processing factors were applied to soybeans - sprouted seeds (0.33x) and peanuts-butter (1.89x). The processing factors are default values from DEEM™.

As shown in **Table 2**, the resulting dietary food exposures occupy **<1% of the Chronic PAD** for all population subgroups included in DEEM. These results should be viewed as conservative (health protective) risk estimates. Refinements such as use of percent crop-treated information and/or anticipated residue values would yield even lower estimates of chronic dietary exposure.

Table 2. Summary: Chronic Dietary Exposure Analysis by DEEM (Tier 1)

Population Subgroup[1]	Exposure (mg/kg/day)	% of Chronic PAD[2]
U.S. Population (Total)	0.000011	<1.0
All Infants (<1 year)	0.000047	<1.0
Nursing Infants	0.000012	<1.0
Non-nursing Infants	0.000061	<1.0
Children (1-6 years)	0.000024	<1.0
Children (7-12 years)	0.000016	<1.0
Males (13 - 19 years)	0.000012	<1.0
Females (>13 years, nursing)	0.000010	<1.0

1 The subgroups listed are: (1) the U.S. Population (total); (2) those for infants and children; and, (3) the most highly exposed of the adult females and males subgroups (in this case, Females, >13 years, nursing)

2 Percent Chronic PAD = (Exposure ÷ Chronic PAD) x 100%.

Note: There are no other subgroup(s) for which the percentage of the Chronic PAD occupied is greater than that occupied by the subgroup U. S. Population (total).

4.2.1.3 Cancer Dietary (Food) Exposure

In accordance with the 1996 Cancer Risk Assessment Guidelines, the HIARC classified diclosulam as a "**not likely human carcinogen**" based on the lack of evidence of carcinogenicity in mice or rats. **Thus, this risk assessment is not required.**

4.2.2 Water Exposure

The Agency currently lacks sufficient water-related exposure data from monitoring to complete a *quantitative* drinking water exposure analysis and risk assessment for diclosulam. Therefore, the Agency is presently relying on computer-generated estimated environmental concentrations (EECs). GENEEC and/or PRZM/EXAMS (both produce estimates of pesticide concentration in a farm pond) are used to generate EECs for *surface* water and SCI-GROW (an empirical model based upon actual monitoring data collected for a number of pesticides that serve as benchmarks) predicts EECs in *ground* water. These models take into account the use patterns and the environmental profile of a pesticide, but do not include consideration of the impact that processing raw water for distribution as drinking water would likely have on the removal of pesticides from the source water. The primary use of these models by the Agency at this stage is to provide a coarse screen for assessing whether a pesticide is likely to be present in drinking water at concentrations which would exceed human health levels of concern.

For any given pesticide, the SCI-GROW model generates a single EEC value of pesticide concentration in *ground* water. That EEC is used in assessments of both acute and chronic dietary risk. It is not unusual for the ground water EEC to be significantly lower than the surface water EECs. The GENEEC model generates several time-based EECs of pesticide concentration in *surface* water, ranging from 0-days (peak) to 56-days (average). The GENEEC peak EEC is used in assessments of acute dietary risk; the GENEEC 56-day (average) EEC is used in assessments of chronic (non-cancer and cancer) dietary risk. PRZM/EXAMS provides longer duration (up to 36-year) values of pesticide concentration in surface water and is mainly used when a refined EEC is needed.

A drinking water level of comparison (DWLOC) is the concentration of a pesticide in drinking water that would be acceptable as a theoretical upper limit in light of total aggregate exposure to that pesticide from food, water, and residential uses. HED uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of monitoring data for a pesticide, the DWLOC is used as a point of comparison against the conservative EECs provided by computer modeling (SCI-GROW, GENEEC, PRZM/EXAMS).

HED back-calculates DWLOCs by a two-step process: exposure [food + (if applicable) residential] is subtracted from the PAD to obtain the maximum acceptable exposure allowed in drinking water; DWLOCs are then calculated using that value and HED default body weight and drinking water consumption figures. In assessing human health risk, DWLOCs are compared to

EECs. When EECs are less than DWLOCs, HED considers the aggregate risk [from food + water + (if applicable) residential exposures] to be acceptable.

Environmental Profile. In soil, diclosulam is mobile (K_{OC} = 55 mL/g.o.c.) and moderately persistent (aerobic soil half-life = 54 days). Diclosulam is expected to be a ground and surface water contaminant.

Estimated Environmental Concentrations (EECs). EFED conducted its Tier 1 screening-level assessments using the simulation models SCI-GROW and GENEEC to generate EECs for ground and surface water, respectively. The modeling was conducted based on the environmental profile and the maximum seasonal application rate proposed for diclosulam (0.032 lb ai/A/year on soybeans).

The EECs are shown in **Table 3**.

Table 3: EFED Estimated Environmental Concentrations (EECs)		
SCI-GROW (μg/L)[1]	**GENEEC (μg/L)**	
0.035 (acute & chronic)	1.54 (peak)	1.28 (56-day average)

1 μg/L = parts per billion or ppb.

4.2.2.1 Acute Dietary (Drinking Water) Exposure

The HIARC did not identify an appropriate toxicological endpoint attributable to a single (acute) dietary exposure. **This risk assessment is not required.**

4.2.2.2 Chronic (Non-Cancer) Dietary (Drinking Water) Exposure

Drinking Water Levels of Comparison (DWLOCs). The DWLOC values are shown in **Table 4**. For each population subgroup listed, the **chronic PAD** (0.05 mg/kg/day) and the chronic dietary (food only) exposure (from Table 2) for that subgroup were used to calculate the chronic DWLOC for the subgroup, using the formulas in footnotes 1 and 2 of Table 4.

Table 4: DWLOCs for Chronic (Non-Cancer) Dietary Exposure to Diclosulam						
Population Subgroup	**Chronic PAD (mg/kg/day)**	**Food Exposure (mg/kg/day)**	**Max. Water Exposure (mg/kg/day)[1]**	**SCI-GROW (μg/L)**	**GENEEC Chronic EEC (μg/L)**	**DWLOC (μg/L)[2,3,4]**
U.S. Population (total)	0.050	0.000011	0.050	0.035	1.28	1.7×10^3
Females 13+ [5]		0.000010	0.050			1.5×10^3
Infants/Children [5]		0.000061	0.050			4.9×10^2
Other [5]		0.000012	0.050			1.7×10^3

1 Maximum Water Exposure (mg/kg/day) = Chronic PAD (mg/kg/day) - [Chronic Food Exposure + Chronic Residential Exposure (mg/kg/day)]. Diclosulam has no registered residential uses.

2 DWLOC (μg/L) = [Maximum water Exposure (mg/kg/day) x body wt (kg)] ÷ [(10^{-3} mg/μg) x water consumed daily (L/day)]. **μg/L = parts per billion.**

3 HED default body weights are: General U.S. Population, 70 kg; Males (13^+ years old), 70 kg; Females (13^+ years old), 60 kg; Other Adult Populations, 70 kg; and, All Infants/Children, 10 kg.

4 HED default daily drinking rates are 2 L/day for Adults and 1 L/day for Children.

5 Within each of these subgroups, the subpopulation with the highest (chronic) food Exposure was selected; namely, **Females (13+/nursing); Non-nursing Infants (<1 year);** and, **Males (13-19 years),** respectively.

4.2.2.3 Cancer Dietary (Drinking Water) Exposure

In accordance with the 1996 Cancer Risk Assessment Guidelines, the HIARC classified diclosulam as a "**not likely human carcinogen**" based on the lack of evidence of carcinogenicity in mice or rats. **Thus, this risk assessment is not required.**

4.3 Occupational Exposure

An occupational and residential risk assessment for diclosulam has been prepared as a separate document (Memo, 12/6/99, J. Arthur, D258377). This assessment is included as Attachment 10. The Executive Summary from that assessment is as follows:

> Only an inhalation toxicity endpoint was chosen for non-dietary exposure to diclosulam. For handlers, daily inhalation exposures were compared to the NOAEL of 10 mg/kg/day from an oral developmental study in rabbits (endpoint: dose-dependent increased abortions, and decreased maternal body weight gain, food consumption, and fecal output) to determine the risk for short-term and intermediate-term inhalation exposures. An endpoint for long-term inhalation exposure was not selected. Results that do not reach a target MOE of 100 present risk concerns. Chronic and/or long-term exposures are not expected for handlers.
>
> An occupational postapplication exposure assessment was not conducted. Following the HED Exposure Science Advisory Council Policy# 008 (March 11, 1999), a decision to

not perform an assessment of postapplication exposure to pre-emergent herbicides is based on two key factors: (1) reentry to perform routine hand labor tasks is not required; and (2) reentry activities that may be necessary tend to result in relatively low levels of dermal exposure because contact with treated media is minimal or infrequent. Because diclosulam is used primarily as a pre-emergent, soil applied herbicide, both of these criteria are met. Further, the only non-dietary route of exposure for which a toxicity endpoint was identified is inhalation, and inhalation is not regarded as a significant route of exposure for postapplication activities, especially for a pre-emergent herbicide.

No chemical-specific handler exposure data were submitted in support of this Section 3 registration. It is the policy of HED to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure Draft Policy # 7, dated 1/28/99).

Exposure to handlers who mix and load diclosulam were assessed wearing long pants, long-sleeved shirt, shoes plus socks, and gloves, and using the product in water-soluble packets (WSP). Also, exposure for handlers who mix and load liquid diclosulam were assessed with the same clothing to cover cases when WSP are premixed before loading into tanks. Handlers who apply diclosulam by groundboom sprayer were assessed in the above clothing (except for the gloves), and using open cab tractors. The MOEs for inhalation, under the above circumstances, range from 250,000 to 1.4 million for handlers. These MOEs are greater than the target (100) and do not exceed HED's level of concern.

The minimum level of personal protective equipment (PPE) for handlers is based on acute toxicity for the end-use product. The Registration Division (RD) is responsible for ensuring that PPE listed on the label is in compliance with the Worker Protection Standard (WPS).

The proposed label for diclosulam (i.e., Strongarm) has a 12-hour restricted entry interval (REI). The technical material has a Toxicity Category III for Acute Dermal, with all other acute studies resulting in Toxicity Category IV. Per the Worker Protection Standard (WPS), a 12-hour restricted entry interval (REI) is required for chemicals classified under Toxicity Category III. Therefore, the REI of 12 hours appearing on the Strongarm label is in compliance with the WPS.

4.4 Residential Exposure

At present, there are no proposed or registered residential uses of diclosulam. However, spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential

source of exposure from the groundboom application method employed for diclosulam. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling as specified in section V. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

4.5 Cumulative Exposure

Diclosulam belongs to the triazolopyrimidine sulfonamide class of herbicides; this class of herbicides also includes the active ingredients cloransulam-methyl and flumetsulam. HED does not currently have data available to determine with certainty whether diclosulam has a common mechanism of toxicity with any other substances. For the purposes of this human health risk assessment, HED has not assumed that diclosulam has a common mechanism of toxicity with other pesticides.

4.6 Endocrine Disruption

The Food Quality Protection Act (FQPA; 1996) requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...." EPA has been working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists to develop a screening and testing program as well as a priority setting scheme to implement this program. The Agency's proposed Endocrine Disrupter Screening Program was published in the Federal Register of December 28, 1998 (63 FR71541). The Program uses a tiered approach and anticipates issuing a Priority List of chemicals and mixtures for Tier 1 screening in the year 2000. As the Agency proceeds with implementation of this program, further testing of diclosulam and its end-use products for endocrine effects may be required.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

5.1 Acute Aggregate Risk (Food + Water)

Acute aggregate risk is the sum of exposures resulting from acute dietary food + acute drinking water. The HIARC did not identify an appropriate toxicological endpoint attributable to a single (acute) dietary exposure. **This risk assessment is not required.**

5.2 Chronic (Non-Cancer) Aggregate Risk (Food + Water)

Chronic (non-cancer) aggregate risk is the sum of exposures resulting from chronic dietary food + chronic drinking water + chronic residential uses. Diclosulam has no proposed or registered residential uses. Therefore, this risk assessment is the aggregate of chronic dietary food + chronic drinking water exposures only. This chronic aggregate risk assessment was conducted for all population subgroups, and the chronic PAD is applied to all population subgroups.

HED used Dietary Exposure Evaluation Model (DEEM™) software for conducting a Tier 1 chronic (non-cancer) dietary (food) exposure analysis. Tier 1 assumptions are tolerance level residues and 100% crop-treated.

As shown in Table 2, the resulting dietary food exposures occupy **up to <1% of the chronic PAD** for all population subgroups included in DEEM™. These results should be viewed as conservative (health protective) risk estimates. Refinements such as use of percent crop-treated information and/or anticipated residue values would yield even lower estimates of chronic dietary exposure.

The EECs (Table 3) provided by EFED for assessing chronic aggregate dietary risk are **0.035 ppb** (in ground water, based on SCI-GROW) and **1.28 ppb** (in surface water, based on GENEEC modeling, 56-day average). The back-calculated DWLOCs (Table 4) for assessing chronic aggregate dietary risk **range from 490 ppb** for the population subgroup with the highest food exposure (Non-nursing Infants) **to 1700 ppb** for the U.S. Population (total) and Males (13 to 19 years old).

The SCI-GROW and GENEEC chronic EECs are less than the Agency's level of comparison (the DWLOC value for each population subgroup) for diclosulam residues in drinking water as a contribution to chronic aggregate exposure. HED thus concludes with reasonable certainty that residues of diclosulam in drinking water will not contribute significantly to the aggregate chronic human health risk and that the chronic aggregate exposure from diclosulam residues in food and drinking water **will not exceed the Agency's level of concern** (100% of the Chronic PAD) for chronic dietary aggregate exposure by *any* population subgroup. EPA generally has no concern for exposures below 100% of the Chronic PAD, because it is a level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to the health and safety of *any* population subgroup. This risk assessment is considered high confidence, conservative, and very protective of human health.

5.3 Cancer Aggregate Risk (Food + Water + Residential)

Cancer aggregate risk is the sum of exposures resulting from chronic dietary food + chronic drinking water + chronic residential uses. In accordance with the 1996 Cancer Risk Assessment Guidelines, the HIARC classified diclosulam as a "**not likely human carcinogen**" based on the lack of evidence of carcinogenicity in mice or rats. **Thus, this risk assessment is not required.**

5.4 Short-, Intermediate-, and Long-Term Aggregate Risks (Food + Water + Residential)

These aggregate risk assessments take into account chronic dietary exposure from food and water (considered to be a background exposure level) plus indoor and outdoor residential exposure. Diclosulam is not proposed or registered for residential uses. **Thus, these risk assessments are not required.**

6.0 DEFICIENCIES/DATA NEEDS

Toxicology

There are no data gaps for diclosulam for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158. However, the Ames mutagenicity test has data gaps (highest dose tested not high enough) and both the acute neurotoxicity study (guideline) and the 1-year neurotoxicity study (non-guideline) are classified unacceptable pending the submission of additional information (Report of the FQPA SFC for diclosulam, 12/3/99, B. Tarplee). A summary of the toxicological data base for diclosulam has been prepared as a separate document. This document is included as Attachment 2. The summary contains detailed information concerning these data deficiencies.

Product Chemistry

None

Residue Chemistry

Note: Minor data gaps in the residue chemistry data base have been cited. The data gaps are discussed in detail in the our review of 12/15/99 (Memo, L. Cheng, D249626). This review is included as Attachment 8. The residue chemistry data gaps are as follows:

1. Revised Section B.

2. Results of Agency method validation for crops.

3. Storage time between sampling and analysis for poultry and eggs in the metabolism study; if the storage time was longer than 6 months, evidence should be provided that the identity of residues had not changed during this period between collection and final analysis.

4. Information on the intervals for which samples and sample extracts were held in frozen storage prior to completion of laboratory analyses in the confined rotational crop study. If samples were stored longer than six months from harvest to definitive sample analysis, data demonstrating the storage stability of ^{14}C-residues in rotational crop matrices should accompany the submitted sample storage history.

5. Analysis of plant metabolism and/or crop field trial samples of peanut and soybean, and drinking water (drinking water data to be requested by EFED) for 2,6-dichloroaniline (2,6-DCA) using a validated method at the parts per billion level; data demonstrating the stability of 2,6-DCA in crop matrices if the samples were stored longer than six months.

Items 1 and 2 (above) should be resolved before tolerances are established. Items 3, 4, and 5 should be made a condition of the registration for the use of diclosulam on peanuts and soybeans.

Occupational and Residential

None

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7.0 ATTACHMENTS

(1) Figure 1. Chemical names and structures of diclosulam and its metabolites identified in primary plant, animal, and rotational crop commodities.
(2) RAB3/HED Registration Toxicology Chapter, G.A. Dannan, 2/2/2000.
(3) HED HIARC Report for diclosulam, G.A. Dannan, 11/9/99.
(4) HED FQPA SFC Report, B. Tarplee, 12/3/99.
(5) RAB3/HED DEEM Report, L. Cheng, 12/22/99.
(6) Tier I Drinking Water EECs, R. Pisigan, Jr. & R. Parker, 11/10/99.
(7) Strongarm* (specimen label).
(8) RAB3/HED Residue Chemistry Review, L. Cheng, 12/15/99.
(9) HED MARC Report, L. Cheng, 12/6/99.
(10) Occupational Residential Exposure Assessment, J. Arthur, 12/6/99.

8.0 DISTRIBUTION

cc **WITH** Attachment(s): RAB3 Reading File, PP#7F4856, PP#6F4784.

cc without Attachment(s): W.D. Wassell, G. Dannan, L. Cheng, J. Arthur.

ATTACHMENT 1

Figure A. Chemical names and structures of diclosulam and its metabolites in plants and animals

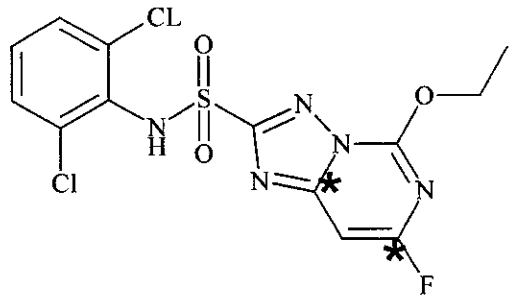
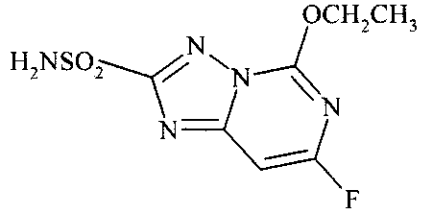
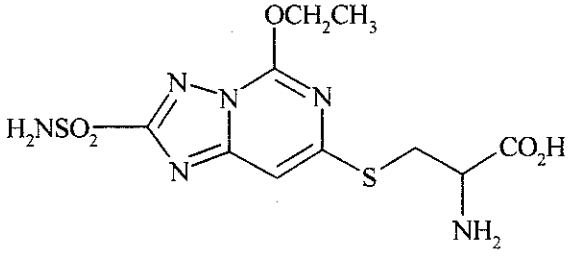
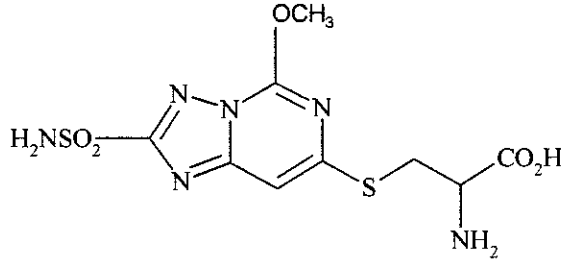
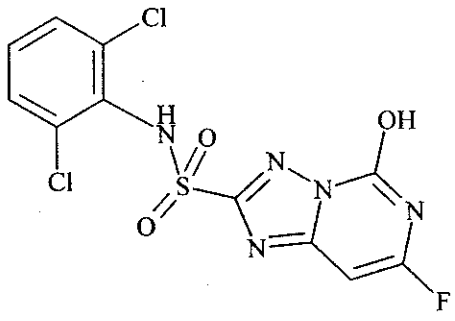
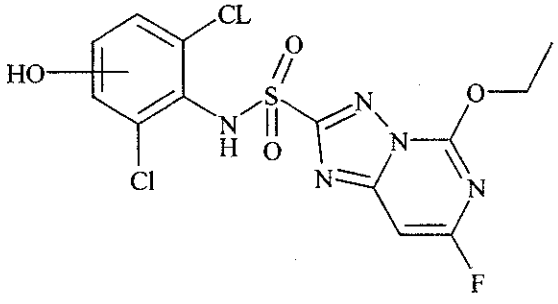
Common Name/Chemical Name	Chemical structure	Matrix
Diclosulam (XDE-564) N-(2,6 dichlorophenyl)-5-ethoxy-7-fluoro-(1,2,4)triazolo[1,5-c] pyrimidine-2-sulfonamide		Hen: liver, muscle, skin, fat, and egg Goat: liver and kidney
ASTP 5-ethoxy-7-fluoro-(1,2,4)triazolo[1,5-c]pyrimidine-2-sulfonamide		Hen: liver, muscle, and egg Goat: kidney
ASTP-Cys (Metabolite C) 7S-[3-aminosulfonyl-5-ethoxy-[1,2,4]triazolo[1,5-c]pyrimidinyl]-cysteine		Soybean: forage
Methyl-ASTP-Cys (Metabolite D) 7S-[3-aminosulfonyl-5-methoxy-[1,2,4]triazolo[1,5-c]pyrimidinyl]-cysteine		Soybean: forage

Figure A. Continued.

Common Name/Chemical Name	Chemical structure	Matrix
5-OH-XDE-564 N-(2,6-dichlorophenyl)-5-hydroxy-7-fluoro-(1,2,4)triazolo [1,5-c]-pyrimidine-2-sulfonamide		Goat: liver
Hydroxy phenyl-diclosulam [a]		Hen: tissue and egg

[a] Tentatively identified by MS analysis. The position of the hydroxyl group is uncertain.

4.3 Prenatal Developmental Toxicity

Adequacy of data base for Prenatal Developmental Toxicity: The data base for prenatal developmental toxicity is considered complete. No additional studies are required at this time. In the rat study, no treatment-related maternal or fetal effects were noted. However, in rabbits a dose-related increase in the number of abortions was observed. Prior to aborting, decreased fecal output, decreased food consumption, and decreased body weight gain were noted in does; the abortions may be secondary to these maternal effects.

870.3700a Prenatal Developmental Toxicity Study - Rat

In a developmental toxicity study (MRID# 43441032), groups of 30 bred Sprague-Dawley Crl:CD®BR rats were administered XDE-564 (Diclosulam; 97.9% a.i.; Lot # DECO-151-86) as a suspension in an aqueous solution of 0.5% METHOCEL™ A4M orally by gavage at doses of 0, 100, 500, or 1000 mg/kg/day on gestation days (GD) 6-15, inclusive, based on the results of a range-finding study (MRID# 43441031). On GD 20, dams were sacrificed, subjected to gross necropsy, and all fetuses examined externally. One-half of the fetuses were examined viscerally, and the other one-half of the fetuses were examined for skeletal malformations/variations.

Maternal survival was 100% for all groups. No treatment-related differences in clinical signs, body weights, body weight gains, or food consumption were noted in any of the treatment groups as compared with the controls. Although the treated groups had statistically significant increases in water consumption as compared with the control group, the toxicological significance of this observation is unclear since there was no dose response and occurred before, during, and after treatment, and were not accompanied by any other reported changes in the dams. No treatment-related differences in liver or kidney weights or in any gross pathological findings were noted in the treated groups. **The Maternal Toxicity NOAEL is equal to or greater than 1000 mg/kg/day, and the Maternal Toxicity LOAEL is greater than 1000 mg/kg/day.**

No dose- or treatment-related, statistically significant effects on pregnancy rates, number of corpora lutea, pre- or postimplantation losses, resorptions/dam, fetuses/litter, fetal body weights, or fetal sex ratios were observed in the treated groups as compared with the controls. One low-dose dam had complete litter resorption.

The combined incidence rates of litters containing fetuses with external, visceral, and skeletal malformations were 1/30, 0/26, 1/28, and 0/28 for the 0, 100, 500, and 1000 mg/kg/day groups, respectively. No treatment-related external, visceral, or skeletal malformations/variations were observed in any litter. **The Developmental Toxicity NOAEL is equal to or greater than 1000 mg/kg/day, and the Developmental Toxicity LOAEL is greater than 1000 mg/kg/day.**

This study is classified as **Acceptable-Guideline** and satisfies the requirements for a developmental toxicity study in rats (83-3a).

870.3700b Prenatal Developmental Toxicity Study - Rabbit

In the initial phase (Phase I) of a developmental toxicity study (MRID 44103524), 20 females, time-mated New Zealand White rabbits/group were administered XDE-564 (97.6% a.i.) as a suspension in an aqueous solution of 0.5% METHOCEL A4M orally by gavage at doses of 0, 65, 325, and 650 mg/kg/day on gestation days (GD) 7-19, inclusive. In a second phase (Phase II), additional groups of 20 bred females were administered dose levels of 0, 10, 65, 325, and 650 mg/kg/day orally by gavage on gestation days (GD) 7-19, inclusive, to examine the repeatability of equivocal results observed in Phase I. The additional dose level of 10 mg/kg/day was added to ensure that a NOEL was established. On GD 28, does were sacrificed, subjected to gross necropsy, and all fetuses examined externally, viscerally, and skeletally for malformations/variations.

A dose-related increase ($p<0.01$) in the number of treatment-related abortions was noted in the treated groups (0, 0, 1, 3, and 7 does in the 0, 10, 65, 325, and 650 mg/kg/day groups, respectively). Prior to aborting, these does generally had decreased fecal output, severely reduced food consumption, and a decrease in body weight gain. These abortions were considered to be an effect of the maternal toxicity noted in these animals. Although evaluation of body weight gain did not reveal statistical significance, the decrements in body weight gain in conjunction with the decreased food consumption and fecal output that occurred in the individual animals is considered an effect of treatment. Because the number of affected does occurred in a dose-related manner ($p<0.01$), the single animal affected in the 65 mg/kg/day group cannot be excluded. Several other intercurrent deaths in these treated groups were attributed to gavage error.

Therefore, the maternal toxicity LOAEL is 65 mg/kg/day based on a dose-related increase in abortions, decreased fecal output, decreased maternal body weight gains and food consumption; the maternal toxicity NOAEL is 10 mg/kg/day.

No statistically significant differences were observed between the treated and control groups for number of corpora lutea/doe, implantations/doe, pre- or postimplantation loss, fetal body weights, or fetal sex ratios. No dose- or treatment-related external, visceral, or skeletal malformations/variations were observed in any fetus.

Therefore, the developmental toxicity NOAEL is 650 mg/kg/day, the highest daily dose, based on lack of developmental toxicity. Developmental toxicity LOAEL is greater than 650 mg/kg/day.

The HIARC, at the meeting of October 26, 1999, considered the dose-related increased abortions as an adverse fetal effect despite the fact that the abortions were probably related to maternal toxicity, the aborted fetuses were viable, and there was no increase in intra-uterine deaths (early or late resorptions). The developmental NOAEL/LOAEL were considered to be 10/65 mg/kg/day based on the dose-related increased abortions.

This study is classified as **Acceptable/guideline** and satisfies the guideline requirements for a developmental toxicity study in rabbits (83-3b).

4.4 Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: The data base for reproductive toxicity is considered complete. No additional studies are required at this time. In a multigeneration rat reproductive study, no systemic toxicity to the parental animals was noted at the dose levels tested up to the limit dose. There were no treatment related findings in the reproductive system of parental animals of either sex. No systemic or developmental toxicity was noted in the offspring of either generation.

870.3800 Reproduction and Fertility Effects - Rat

In a multigeneration reproduction study (MRID# 44207402), groups of CD rats (30 per sex, per dose) from Charles River Breeding Laboratory, Kingston, NY, received 0, 50, 500, 750 or 1000 mg/kg/day XDE-564 (Diclosulam, XR-564, XRD-564; Purity: 97.6%; Lot No.: TSN100168) in the diet for two successive generations; due to the lack of toxicity noted with this compound the 750 mg/kg/day dose group was dropped. Each rat on study was observed twice daily for mortality, morbidity and moribundity, once daily for changes in behavior or demeanor or overt signs of toxicity. Weekly thorough clinical physical examinations were conducted on each P1 and P2 animal. All P1 animals had body weights and feed consumption recorded weekly during the 10-week pre-breeding treatment period with body weights for males recorded weekly throughout the course of the study. Sperm positive females were weighed on Days 0, 7, 14 and 21 of gestation. Females that delivered litters were weighed on Days 1, 4, 7, 14, and 21 of lactation. Feed consumption was not measured in males or females during the breeding period, but following this period weekly feed consumption was measured in males and in sperm positive females during gestation. After parturition, feed consumption was measured on days 1, 4, 7, 11, 14, 17, 19 and 21 of lactation. Females were observed for evidence of parturition. The date of delivery was recorded as the first day the litter was observed and was designated as lactation day 0. All litters were examined as soon as possible after delivery. The following data were recorded on each litter: litter size on the day of parturition (lactation day 0), the number of live and dead pups on days 0, 1, 4, 7, 14, and 21 postpartum, and the sex and weight of each pup on days 1, 4 (before and after culling), 7, 14, and 21 of lactation. Any visible physical abnormalities or demeanor changes in the neonates were recorded during the lactation period. The F1 and F2 litters were culled to 8 pups on day 4 postpartum. All litters were weaned on day 21 postpartum. A complete necropsy of all P1 and P2 adults was performed. The eyes were examined. Data from previous studies with this compound in Fischer 344 rats showed possible effects in the liver and kidney, therefore terminal body weights and liver and kidney weights were recorded in the P2 adults for comparison of possible liver and kidney effects in the CD (Sprague-Dawley derived) strain of rat used in this study. The organ-to-body weight ratios were calculated for the P2 adults. Histologic examination of potential target organs and reproductive tissues, and all gross lesions was performed on the control and high dose groups. Prior to weaning, 10 pups/sex/dose level

from the F1 and F2 litters were randomly selected for a complete necropsy.

No systemic toxicity to the parental animals was noted at the dose levels tested up to the limit dose. There were no treatment related findings in the reproductive system of animals of either sex. **The Parental (Paternal/Maternal) Systemic Toxicity NOAEL is equal to or greater than 1000 mg/kg/day and the Parental (Paternal/Maternal) Systemic Toxicity LOAEL is greater than 1000 mg/kg/day.**

No systemic or developmental toxicity was noted in the offspring of either generation. **The Offspring Systemic/Developmental Toxicity NOAEL is equal to or greater than 1000 mg/kg/day and the Offspring Systemic/Developmental Toxicity LOAEL is greater than 1000 mg/kg/day.**

No effects were noted on reproductive parameters. **The Reproductive Toxicity NOAEL is equal to or greater than 1000 mg/kg/day and the Reproductive Toxicity LOAEL is greater than 1000 mg/kg/day.**

This study is classified as Acceptable-Guideline and satisfies the requirements (OPPTS 870.3800, OPP §83-4) for a multigeneration reproduction study in rats.

4.5 Chronic Toxicity

Adequacy of data base for chronic toxicity: The data base for chronic toxicity is considered complete for risk assessment. No additional studies are required at this time. In a chronic toxicity/oncogenicity study in the rat, the kidney is identified as a target organ. Changes in clinical chemistry and urinalysis parameters (indicative of altered renal tubule function) included increased creatinine, decreased urine specific gravity, increased urine volume, and decreased urinary protein concentration. Dose-related microscopic renal tubular pathology was also noted. Body weight gain was decreased 7-20% in treated animals compared to controls. The kidney was also a target organ in a mouse carcinogenicity study. Among the observed kidney effects were reduced vacuolization in the tubular epithelium, lower absolute and relative kidney weights, and focal dilatation with hyperplasia of the epithelial lining in the cortical tubules.

870.4100a (870.4300) Chronic Toxicity – Rat

In a combined chronic toxicity/oncogenicity study (MRID 44103525), XDE-564 (97.6% a.i.; Lot Number TSN 100168, DECO 151-86) was administered in the diet to 60 male and 60 female CDF®(F-344)CrlBR rats per group at doses of 0, 5, 100, or 400 mg/kg/day for up to slightly over 104 weeks except for 10 animals per sex per dose that were sacrificed at 52 weeks for interim evaluation and neurotoxicity assessment. The neurotoxicity results were reported separately (MRID 44103526) and will be evaluated in another DER.

Survival was unaffected by the treatment. Significant ($p<0.05$) treatment-related decreases in

body weight and body weight gain were demonstrated in both sexes when fed XDE-564 at 100 and 400 mg/kg/day. Although the effects on total body weight did not approach a 10% reduction from control, the reduction in body weight gain was often in the range of 7–20% or more. Food consumption was similar in treated and control groups of both sexes, with the exception of the 400 mg/kg/day males, for which it was often from 5–10% lower.

There were slight (<5%) but statistically significant reductions ($p \leq 0.05$) in RBCs, hemoglobin, and hematocrit in both sexes at the high dose level. One such reduction was also observed in female rats of the 100 mg/kg/day group. The hematological effects observed are considered to be of no biological significance.

There were changes in several clinical chemistry and urinalysis parameters indicative of altered renal tubule function. Serum creatinine was increased (approximately 13%) in males in the 100 and 400 mg/kg/day groups and in females of the 400 mg/kg/day group at weeks 27, 52, 78 and/or 104. The mean urine specific gravity readings were slightly lower (although statistically significant) in the 100 and 400 mg/kg/day males and females at weeks 27, 52, 78 and/or 105. Other renal changes include increased urine volume and decreased urinary protein concentration in the mid- and high-dose groups of both sexes. These changes are considered to be a mild effect of the administration of XDE-564 on the kidney (mild tubular alterations). There were no findings of toxicological importance regarding gross pathology and organ weights.

A notable microscopic lesion in rats fed XDE-564 for 52 or 104 weeks was a subtle change in the kidneys which mostly affected the tubules of the corticomedullary region. The most salient feature of this renal alteration, with little or questionable toxicological significance, was a patchy to diffuse distribution change in the cytologic character and architecture of renal tubules, mostly within the corticomedullary junction. The incidence of tubular changes in the kidney was 4, 11, 41, and 77% in males and 4, 10, 69, and 82% in females in the 0, 5, 100 and 400 mg/kg/day groups, respectively. The corticomedullary tubular changes might well account for the altered renal tubule function. The incidence of hyperplasia of the pelvic epithelium was also dose-dependently increased among males and, compared to the control group (50%), this lesion was statistically significantly (≤ 0.05) increased in the mid- and high-dose male groups (72% and 85%, respectively).

No effects attributable to the test material and of biological or toxicological importance were observed at doses of 5 mg/kg/day.

The LOAEL is 100 mg/kg/day in both sexes based upon statistically significant decreases in body weight gain, increases in creatinine (males), decreases in urinary specific gravity and protein (both sexes), increased urine volume and renal tubule changes (both sexes) and increased incidence of pelvic epithelium hyperplasia (males). The absence of significant treatment-related effects identifies a NOAEL of 5 mg/kg/day in both sexes.

No evidence of carcinogenicity was observed in rats fed XDE-564 at doses of 5, 100, or 400

mg/kg/day for slightly over 104 weeks. Dosing was considered adequate because of the decreases in body-weight gain in both sexes fed 400 mg/kg/day.

This chronic/oncogenicity study in rats is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a combined chronic toxicity/oncogenicity study in rats (§83-5).

870.4100b Chronic Toxicity - Dog

In a 12-month dietary study (MRID 44207401), Diclosulam (Lot# DECO-151-86, 97.6% purity) was administered in the feed to 4 beagle dogs/sex/dose at dietary doses of 0, 2, 10, or 25 mg/kg/day. The dose levels were chosen based on a previous subchronic toxicity study in dogs (MRID 43450401) in which there were serious health and palatability problems at 100 mg/kg/day, the highest dose tested (HDT), and some of the effects (e.g., emaciation and negative weight gain) persisted after the HDT was reduced to 50 mg/kg/day.

No deaths occurred and there were no treatment-related clinical signs. There were no effects of treatment on body weight, body weight gain, food consumption, food efficiency, clinical chemistry or hematology parameters, or absolute or relative organ weights. There were no treatment-related gross or microscopic lesions. Nonetheless, the choice of the dose levels, based on the earlier subchronic study, is considered reasonable.

The NOAEL in both male and female dogs is 25 mg/kg/day based on the absence of effects of any kind. As this was the highest dose tested, a LOAEL for either male or female dogs was not attained.

This study, when combined with the previous subchronic toxicity study (MRID 43450401), is considered **Acceptable/guideline** as a chronic (12-month) feeding study and does fulfill the FIFRA guideline requirements for a chronic oral toxicity study in dogs (83-1b).

4.6 Carcinogenicity

Adequacy of data base for Carcinogenicity: The data base for carcinogenicity is considered complete. No additional studies are required at this time. There is no evidence of carcinogenic potential in either the rat or the mouse.

870.4200a Carcinogenicity Study - rat

This study (MRID No. 44103525) is presented in the Chronic Toxicity Section (see 870.4100a) above.

870.4200b Carcinogenicity (feeding) - Mouse

In a carcinogenicity study (MRID# 44192602), Diclosulam (97.6%) was administered to 60

B6C3F1/CrlBR VAS/Plus® mice/sex/dose in the diet at dose levels of 0, 50, 100, 250 and 500 mg/kg/day for at least 104 weeks. Ten animals/group were designated for interim sacrifice after 52 weeks of treatment. Parameters measured included clinical examinations, body weights, food consumption, ophthalmologic examination, hematology, organ weights, gross necropsy, and histopathology.

There were no treatment-related effects on survival, food consumption and clinical observations. Body weight was decreased at several time points 3-6% in the male and female 500 mg/kg/day groups. Subcapsular (or more severe) cataracts were observed in all treated male groups. There was reduced vacuolization of the kidney tubular epithelium in all male dose levels at the interim and terminal sacrifices which correlated with a statistically significant lower absolute and relative kidney weights in males in the 250 and 500 mg/kg/day groups at the interim sacrifice and in males in the 100, 250 and 500 mg/kg/day groups in the terminal sacrifice. Focal dilatation with hyperplasia of the lining epithelium of cortical tubules of the kidney was seen in a dose-dependent manner among the females in the 100, 250 and 500 mg/kg/day groups.

The LOAEL in males is 50 mg/kg/day based on an increase in subcapsular cataracts and decreased vacuolization in the kidney tubular epithelium. The NOAEL was not determined in males. In females, the NOAEL is 50 mg/kg/day based on the increased incidence of hyperplasia in the kidney tubule epithelium with dilatation at doses equal to or greater than the LOAEL of 100 mg/kg/day. At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls.

This carcinogenicity study in the mouse satisfies the requirement for a carcinogenicity study (83-2b) in mice.

4.7 Mutagenicity

Adequacy of data base for Mutagenicity: The data base for Mutagenicity is considered inadequate based on both pre 1991 or 1991 mutagenicity guidelines. The bacterial reverse mutation assay is considered unacceptable since diclosulam was not tested at an adequately high concentration.

Gene Mutation

Guideline 870.5100 Bacterial reverse mutation assay (Ames Test) MRID 43441035 Unacceptable	Not tested at high enough concentrations to evaluate mutagenicity. Not mutagenic with or without S9 activation at 5 µg/plate and less.
Guideline 870.5300 *In vitro* mammalian cell gene mutation assay (CHO/HGPRT) MRID 43441034 Acceptable	Negative with or without S9 up to 500 µg/mL, a dose considered to be above the limit of solubility for diclosulam.

Cytogenetics

Guideline 870.5375, *In vitro* mammalian chromosome aberration (rat lymphocytes) MRID 43441036 Acceptable	Negative with or without S9 up to 500 µg/mL (higher doses formed a precipitate). No cytotoxicity was seen.
Guideline 870.5395, Mammalian erythrocyte micronucleus test (mouse) MRID 43441033 Acceptable	Negative. Test compound at 1250, 2500, or 5000 mg/kg (oral gavage) with 24, 48, and 72 hour sacrifices did not induce the formation of micronuclei in polychromatic erythrocytes from bone marrow.

4.8 Neurotoxicity

Adequacy of data base for Neurotoxicity: These studies are not required at this time. No evidence of neurotoxicity was observed in an acute neurotoxicity rat study; however, the study is considered unacceptable due to inadequate positive control data and pending submission of untransformed motor activity data. In a chronic oral neurotoxicity study in rats, decreased hind limb grip strength was observed in males at the mid- and high doses of 100 and 400 mg/kg/day, respectively. However, this study was also considered unacceptable due to inadequate positive control data and insufficient procedural information.

870.6200 Acute Neurotoxicity Screening Battery

In an acute neurotoxicity study (MRID # 44192601), rats (10/sex/group) received a single dose of XDE-564 (97.6% a.i.) by gavage (in methyl cellulose). Doses were 0, 200, 1000, or 2000 (a limit dose) mg/kg for both sexes. Clinical observations were recorded twice daily. Evaluation during the two-week study period included body weights, functional observational battery (FOB), motor activity and neuropathology. The FOB consisted of hand-held and open-field observations, grip performance, rectal temperature and landing foot splay testing. Animals were evaluated by FOB and motor activity assay once prior to exposure, on day 1 (beginning approximately 5 hours after dosing), and on days 8 and 15 of the study period. Body weights were determined on days -7,1,2,8 and 15 relative to the day of dosing (day 1). Cholinesterase inhibition was not evaluated. At study termination on day 16, 5 rats/sex/group were perfused intracardially with glutaraldehyde/paraformaldehyde, and histopathological evaluation of peripheral and central nervous system tissue was performed on animals from the control and high dose groups only.

No evidence of neurotoxicological effects were observed at any of the dose levels. Furthermore, there were no compound-related effects in mortality, morbidity, clinical signs, body weight, FOB, motor activity or neuropathology.

Additionally, a gavage range-finding study (MRID # 44103522) was conducted to determine the benchmark dose (3 rats/sex). This dose-ranging study is acceptable.

A positive control data were submitted as three separate appendices, with different test chemicals, procedures, and dosage regiments. The opinion of the EPA reviewer is that the three studies were incompatible with the current study (MRID # 44192601). Consequently, the positive control data are rejected.

The LOAEL is not observed, based on lack of toxicity at any of the dose levels. The tentative NOAEL is 2000 mg/kg for both sexes, pending submission of requested information.

This acute neurotoxicity study is classified **Unacceptable/Guideline** pending submission of untransformed motor activity data and sufficient positive control data to satisfy EPA reviewers. This study does not satisfy the guideline requirement for an acute neurotoxicity study (81-8) in rats.

Nonguideline Chronic Neurotoxicity Screening Battery

This study was part of a 104-week chronic toxicity/oncogenicity dietary study which included a set of rats designated for a 52-week neurotoxicity study. Only data relating to the neurotoxicity portion of this study will be discussed in this report.

In a chronic oral neurotoxicity study (MRID 44103526), groups of 12 CDF® (F-344) CrlBR rats/sex/group were administered XDE-564 (Purity 97.6%) in the diet for 52 weeks at target levels of 0 (control), 5, 100, or 400 mg/kg/day. The actual mean achieved doses were 5.2, 102.6, and 419.9 mg/kg/day for males, and 5.2, 104.8, and 413.4 mg/kg for females, respectively. Body weights and food consumption were recorded weekly during the first 14 weeks of the study and every fourth week thereafter. Functional observational battery (FOB), automated auditory startle, and locomotor activity (LMA) testing were performed prior to administration and after 3, 6, 9, and 12 months of treatment. Ophthalmoscopic examinations were performed during week 52. At study termination, six animals/sex/dose were sacrificed, perfusion fixed, and designated tissues of the nervous system were processed for microscopic neuropathological evaluation. Tissues from control and high dose groups were examined histopathologically

There were no mortalities prior to scheduled termination. Statistically significant decreases ($p<0.05$) in body weight were observed throughout the study among males and females treated with 400 mg/kg, however the difference from control was consistently less than 7%, and these decreases are not considered toxicologically relevant. Clinical observations showed increased incidence of urine staining in females at 100 and 400 mg/kg/day dose levels, starting as early as week 5 at the high dose. There was also a slight increase in incidence of urine staining in males at the high dose only. During the FOB assessment females treated at the highest dose displayed increased incidences of urine staining. There was also a statistically significant decrease in hind

limb grip strength in mid dose (week 39 only) and high dose (weeks 26 and 39) males. No other treatment related signs of neurotoxicity were observed during the study. No neuropathological endpoints attributable to administration of the test material were observed during the histological examinations of the peripheral or central nervous systems of these animals at any exposure concentration, however peripheral nervous system tissues were not processed according to Guideline procedures.

Due to the lack of procedural information (particularly with regard to the auditory startle and locomotor activity data), and the lack of positive control data, and other study deficiencies, no definitive conclusions can be reached at this time.

Due to study deficiencies (including lack of positive control data and insufficient procedural information), a NOAEL/LOAEL could not be determined for this study. Upon submission of requested additional information, NOAEL/LOAEL levels will be reassessed.

This study is classified **Unacceptable/nonguideline** and does not satisfy the Subdivision F guideline requirement for a subchronic oral neurotoxicity study (§82-7) in rats. This study may be upgradable upon receipt of requested information for this study, but will not satisfy the guideline for a subchronic neurotoxicity study because effects were not evaluated at the 4 and 8 week time points.

4.9 Metabolism

Adequacy of data base for metabolism: The data base for metabolism is considered to be complete. No additional studies are required at this time. Following oral treatment with a low dose of the test material, the apparent absorption (evidenced by renal excretion) was ~40% among male rats and ~65% among females. The compound was rapidly excreted in the urine and feces primarily as unchanged parent and a hydroxy-phenyl metabolite. At the higher dose, bioavailability was apparently decreased in both sexes with >81% of the dose eliminated into the feces with ~78% of the dose as unchanged parent. In both dose groups, sex-related differences were noted and included higher levels of renal excretion of parent by females, more extensive metabolism by males, and higher levels of residual label in the liver of males.

870.7485 Metabolism - Rat

In a rat metabolism study (MRID 44103527), [U-phenyl-^{14}C]XR-564 (≥98 % a.i.) was administered to five Fischer 344 rats/sex/dose as a single oral (gavage) dose at 5 or 500 mg/kg or as a single oral dose at 5 mg/kg following a 14-day pretreatment with non-radiolabeled XR-564 at 5 mg/kg. In addition, four male Fischer 344 rats were administered a single oral dose of [^{14}C-triazolo-pyrimidinyl]XR-564 at 5 mg/kg.

Within 72 hours of dosing with [^{14}C]XR-564, 89.6-95.0% of the administered dose was recovered from both males and females. A preliminary study using rats dosed at 500 mg/kg

indicated that <0.1% of the dose was recovered in expired air. Sex-related differences in the excretion of radioactivity and the metabolism of [^{14}C]XR-564 were apparent at the low dose level, but were less evident at the high dose level. Both pretreatment with XR-564 and the position of the ^{14}C-label within the molecule had no effect on the rate or pattern of excretion, or on the metabolism of XR-564.

In all dose groups, excretion of radioactivity was relatively rapid, with 73.7-86.9% of the dose being excreted in the urine and feces within 24 hours of dosing. The half-life ($t_{½}$) for urinary elimination of radioactivity was 7.6-9.6 hours for low-dose groups and 10.8-12.1 hours for high-dose animals.

Low-dose males excreted approximately equal amounts of the administered dose in the urine (39.4-44.4% dose) and feces (42.2-47.6% dose). The major metabolite in excreta of low-dose males was OH-phenyl-XR-564 (34.5-43.8% dose), which was excreted primarily in the feces (24.4-34.2% dose). Parent was excreted at lower levels (12.8-23.5% dose), with approximately equal amounts being excreted in the urine (9.0-11.4% dose) and feces (2.8-12.1% dose). The N-acetyl cysteine conjugate of XR-564 (5.2-5.5% dose) and sulfate/glucuronide conjugate(s) of OH-phenyl-XR-564 (6.3-6.9% dose) were both major urinary metabolites in males, while the S-oxide of the cysteine conjugate (0.4-0.7% dose) was a minor urinary metabolite.

In contrast, low-dose females excreted ~3x the amount of radioactivity in urine (62.1-68.1% dose) as in feces (22.9-26.4% dose). Dosed radioactivity was excreted primarily as parent (39.7-47.9% dose), with the majority of parent being excreted renally (32.2-33.7% dose). The amount of OH-phenyl-XR-564 in the urine of females (10.7-13.6% dose) was comparable to the levels in urine of males (7.2-10.6% dose), but the amounts of OH-phenyl-XR-564 in feces were 4-5x lower in females (6.7-8.1% dose) than in males (24.4-34.2% dose). Sulfate/glucuronide conjugates of OH-phenyl-XR-564 were not detected in excreta of females, but females had higher levels in the urine of the N-acetyl cysteine conjugate of XR-564 (8.5-10.6% dose) and its S-oxide (4.5-6.3% dose), than males.

Increasing the dose to 500 mg/kg, decreased the bioavailability of [^{14}C]XR-564. High-dose males and females eliminated 81.9-84.9% of the dose in the feces, nearly all of which was unchanged parent (78.3-78.8% dose). Although renal excretion was decreased compared to the low-dose group, high-dose females still showed higher levels of renal excretion (11.6% dose) than high-dose males (6.2% dose). In addition to parent, OH-phenyl-XR-564 was identified in excreta of males (4.6% dose) and females (1.8% dose). All other metabolites in urine and feces of high-dose rats accounted for ≤1.1% of the dosed radioactivity.

Radioactivity remaining in the carcass and tissues at 72 hours post-dose accounted for ≤1.1% of the dose for animals dosed with [U-phenyl-^{14}C]XR-564, with males (0.3-1.1% dose) retaining slightly more radioactivity than females (0.2-0.7% dose). In each dose group, the concentration of radioactivity in tissues and blood was also slightly higher (1-1.8x) in males than in females, with the exception of liver. Levels of radioactivity in the liver were ~4x higher in males than

females from the low-dose groups, and ~2x higher in males than females from the high-dose group. For both sexes in each [U-phenyl-^{14}C]XR-564 dose group, concentrations of radioactivity were highest in kidneys, blood, and liver (males only) and lowest in brain, fat, spleen, and muscle. Pretreatment had no effect on the concentration of radioactivity in tissues and blood, and increasing the dose level by 100x increased the concentration of radioactivity in tissues by only ~20-50x, supporting the conclusion that bioavailability was limited at the high dose level.

The concentration of radioactivity in tissues and blood was the only parameter affected by the position of the ^{14}C-label within the parent molecule. With the exceptions of liver, muscle, skin, and testes, males dosed with [^{14}C-triazolo-pyrimidinyl]XR-564 had substantially higher (2.6-28x) concentrations of radioactivity in blood and tissues than males dosed with [U-phenyl-^{14}C]XR-564. The distribution of radioactivity among tissues also differed. In males dosed with [^{14}C-triazolo-pyrimidinyl]XR-564, radioactivity was highest in the blood, kidneys, bone, lung and spleen and was lowest in the muscle, skin, brain and testes.

The sex-related differences observed in the metabolism of XR-564 (higher levels of renal excretion of parent by females, more extensive metabolism of XR-564 by males, and the relatively higher concentrations of radioactivity in the liver of males) may be related to the differences noted between the sexes in the 13-week dietary toxicity study, in which histopathological alterations were observed in livers of males dosed at 100-1000 mg/kg/day and females dosed at 1000 mg/kg/day.

This study is classified **acceptable (§85-1)** and satisfies the Tier 1 requirements for a metabolism study.

4.10 Special/Other Studies

Two-week preliminary dietary feeding studies (non guideline) were conducted in F344 rats (MRID 43441030) and B6C3F1 mice (MRID 43441028). Doses were 0, 100, 500, or 1000 mg/kg/day in both studies.

Effects in rats were limited to males and included increased cecal weight in high-dose males, and increased relative liver weights in the mid- and high-dose males.

Increased alkaline phosphatase activities were observed in high-dose male and female mice. Very slight focal renal tubule degeneration and decreased hepatocyte vacuolation were observed in female mice.

5.0 HAZARD ENDPOINT SELECTION

On October 26, 1999 (HED Doc. 013847, dated Nov. 9, 1999), the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of **Diclosulam**, established a Reference Dose (RfD) and selected the toxicological

endpoints for acute dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to Diclosulam as required by the Food Quality Protection Act (FQPA) of 1996. The FQPA Safety Factor Committee met on November 15, 1999 (HED Doc. No. 013875, dated Dec. 3, 1999), to evaluate the hazard and exposure data for diclosulam and recommended that the FQPA Safety Factor (as required by the Food Quality Protection Act of August 3, 1996) be removed (1x) in assessing the risk posed by this chemical.

5.1 Reference Doses

5.1.1 Acute Reference Dose

Study Selected: None
Comments about Study/Endpoint: There were no appropriate toxicological effects attributable to a single exposure observed in oral toxicity studies. This includes maternal effects in the developmental toxicity studies in rats and rabbits and effects in a rat acute neurotoxicity study. Therefore, a dose and an endpoint were not selected for this risk assessment.

This risk assessment is NOT required.

5.1.2 Chronic Reference Dose (RfD)

Study Selected: 2-Year Feeding Oncogenicity Study in Rats. §870.4300, MRID No. 44103525
Dose/Endpoint for establishing the RfD: NOAEL = 5 mg/kg/day based on decreased body weight gain and renal clinical and histopathological changes at 100 mg/kg/day (LOAEL).

Uncertainty Factor(s): 100 (10x for inter-species extrapolation and 10x for intra-species variability)

$$\textbf{Chronic RfD} = \frac{\textbf{5 mg/kg/day (NOAEL)}}{\textbf{(100)}} = \textbf{0.05 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor: The lowest NOAEL in the most sensitive species following chronic exposure was utilized.

This risk assessment is required.

5.2 Dermal Exposure

5.2.1 Dermal Absorption

Dermal Absorption Factor: 6.5 % (Estimated)

There is no dermal absorption study with Diclosulam. However, the dermal absorption rate was estimated from the results of a 21-day dermal toxicity (MRID 44103523) and a developmental toxicity (MRID 44103524) studies in rabbits. In the developmental toxicity study, the maternal NOAEL/LOAEL were 10/65 mg/kg/day based on a dose-related increased abortions and decreased fecal output, maternal body weight gains, and food intake. In the 21-day rabbit dermal toxicity study there were no treatment-related clinical signs, or effects on body weight, food consumption, hematology, clinical chemistry, ophthalmology, or organ weights. The systemic and dermal NOAEL is the limit dose of 1000 mg/kg/day and LOAEL is unidentified. Assuming the dermal LOAEL is the limit dose of 1000 mg/kg/day, an approximate dermal absorption rate of 6.5% was derived by relating the LOAELs ratio from the oral and dermal studies (65/1000 x 100).

5.2.2. Short-Term Dermal (1-7 days)

Study Selected: None
Dose and Endpoint for Risk Assessment: N/A
Comments about Study/Endpoint: In a 21-day rabbit dermal toxicity study, there was no systemic toxicity at the limit dose of 1000 mg/kg/day (MRID 44103523).

This risk assessment is **NOT** required.

5.2.3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: None
Dose/Endpoint for Risk Assessment: N/A
Comments about Study/Endpoint: In a 21-day rabbit dermal toxicity study, there was no systemic toxicity at the limit dose of 1000 mg/kg/day (MRID 44103523).

This risk assessment is **NOT** required.

5.2.4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: None

Dose and Endpoint for Risk Assessment: N/A
Comments about Study/Endpoint: It is estimated that there will be one Diclosulam application per season. Therefore, the HIARC concluded that there is no long-term dermal exposure/risk potential.

This risk assessment is **NOT** required.

If future application of diclosulam results in chronic dermal exposure then the dermal absorption factor will be required for the dermal risk assessment since oral doses would be selected for this exposure scenario.

5.3 Inhalation Exposure (Any Time Period)

5.3.1

Based on the inhalation LC_{50}> 5.04 mg/L, Diclosulam is placed in Toxicity Category IV. The use pattern (1 application/season) does not indicate a concern for potential long-term inhalation exposure. Since only an acute inhalation toxicity study was available, the HIARC recommended that a route-to-route extrapolation should be made using the rabbit oral developmental study.

Study Selected: Rabbit Oral Developmental Study (MRID No. 44103524)
Dose and Endpoint for Risk Assessment: Maternal/developmental NOAEL = 10 mg/kg/day based on dose-dependent increased abortions and decreased maternal body weight gain, food consumption and fecal output at 65 mg/kg/day (LOAEL).
Comments about Study/Endpoint: Convert the inhalation exposure component (i.e., μg a.i./day) using a 100% absorption rate (default value) and an application rate to an **equivalent oral dose** (mg/kg/day); this dose should then be compared to the oral NOAEL of 10 mg/kg/day to calculate the MOEs for short- and intermediate-terms.

5.3.2. MOEs for Occupational/Residential Exposure Risk Assessments

An MOE of 100 is adequate for occupational exposure risk assessments. There are no residential uses.

5.3.3. Recommendation for Aggregate Exposure Risk Assessments

Aggregate exposure risk assessment will be limited to the chronic exposure (food + water) since doses and end-points were not identified for acute dietary or short-term and intermediate-term dermal or inhalation exposure risk assessments.

5.4 Classification of Carcinogenic Potential

The HIARC Committee concluded:

Carcinogenicity studies in rats (§870.4300, MRID No. 44103525) and mice (§870.4200, MRID No. 44192602) were acceptable. There was no evidence of carcinogenicity in either species.

In accordance with the 1996 Cancer Risk Assessment Guidelines, the HIARC classified Diclosulam as a "**not likely human carcinogen**" based on the lack of evidence of carcinogenicity in mice or rats.

6.0 FQPA CONSIDERATIONS

6.1 Special Sensitivity to Infants and Children

Based on the available data, the HIARC concluded that there is no indication of increased susceptibility of rats or rabbits to *in utero* and/or to post natal exposure to Diclosulam.

6.2 Recommendation for a Developmental Neurotoxicity Study

Based on the lack of evidence of neurotoxicity/neuropathology and no alterations in the fetal nervous system as well as no increased susceptibility, the HIARC **did not recommend** a developmental neurotoxicity study in rats for Diclosulam.

6.3 FQPA Safety Factor Committee Recommendation

The FQPA Safety Factor Committee met on November 15, 1999 (HED DOC. No. 013875, dated 12-3-99) to evaluate the hazard and exposure data for diclosulam and recommended that the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996) be removed (1x) in assessing the risk posed by this chemical. The rationale for removing the safety factor included: 1) The toxicology database is complete for the assessment of the effects following *in utero* and/or postnatal exposure to diclosulam; 2) The toxicity data provided no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure; 3) A developmental neurotoxicity study is not required by HIARC; and 4) The exposure assessment approach will not underestimate the potential dietary (food and water) exposures for infants and children resulting from the use of diclosulam (no residential exposure is expected).

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8.0 APPENDICES
Tables for Use in Risk Assessment

8.1 Toxicity Profile Summary Tables

8.1.1 Acute Toxicity Table - See Section 4.1

8.1.2 Subchronic, Chronic and Other Toxicity Table

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents	43441029 (1993) Acceptable/guideline M & F: 0, 50, 100, 500, 1000 mg/kg/day	NOAEL: Males: 50 mg/kg/day; Females: 100 mg/kg/day LOAEL Males = 100 mg/kg/day based on increased relative liver weight, hepatocellular hypertrophy, multifocal liver necrosis. LOAEL Females = 500 mg/kg/day based on increased relative liver and brain weights, decreased body weight.
870.3150 90-Day oral toxicity in nonrodents	43450401 (1992) Acceptable/guideline M & F: 0, 5, 25, 100/50 mg/kg/day	NOAEL = 5 mg/kg/day LOAEL = 25 mg/kg/day based on histopathological liver lesions.
870.3200 21/28-Day dermal toxicity	44103523 (XDE-564) & 44103514 (BF-309) (1996) Acceptable/guideline M & F: 0, 100, 500, 1000 mg/kg/day	NOAEL = 1000 mg/kg/day LOAEL = not identified
870.3250 90-Day dermal toxicity	NA	NA
870.3465 90-Day inhalation toxicity	NA	NA
870.3700a Prenatal developmental in rodents	43441032 (1994) Acceptable/guideline F: 0,100, 500, 1000 mg/kg/day	**Maternal** NOAEL ≥1000 mg/kg/day LOAEL >1000 mg/kg/day based on no effects. **Developmental** NOAEL ≥1000 mg/kg/day LOAEL >1000 mg/kg/day based on no effects.
870.3700b Prenatal developmental in nonrodents	44103524 (1996) Acceptable/guideline F: 0, 10, 65, 325, 650 mg/kg/day	**Maternal** NOAEL = 10 mg/kg/day LOAEL = 65 mg/kg/day based on increased abortions, decreased fecal output, decreased maternal body weight gains and food consumption. **Developmental** NOAEL = 10 mg/kg/day LOAEL = 65 mg/kg/day based on increased abortions.
870.3800 Reproduction and fertility effects rats	44207402 (1996) Acceptable/guideline M & F: 0, 50, 500, 750, 1000 mg/kg/day	**Parental/Systemic** NOAEL ≥1000 mg/kg/day LOAEL >1000 mg/kg/day based on no effects. **Reproductive** NOAEL ≥1000 mg/kg/day LOAEL > 1000 mg/kg/day based on no effects. **Offspring** NOAEL ≥1000 mg/kg/day LOAEL > 1000 mg/kg/day based on no effects.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4300 Chronic toxicity rodents	44103525 (1996) Acceptable/guideline M & F: 0, 5, 100, 400 mg/kg/day	NOAEL = 5 mg/kg/day LOAEL = 100 mg/kg/day based on decreased body weight gain, urinalysis parameters, and renal tubule changes.
870.4100 Chronic toxicity dogs	44207401 (1996) Acceptable/guideline M & F: 0, 2, 10, 25 mg/kg/day	NOAEL: 25 mg/kg/day LOAEL: not identified; dose selection reasonable and study acceptable when combined with the subchronic toxicity dog study (MRID 43450401).
870.4300 Carcinogenicity rats	44103525 (1996) Acceptable/guideline M & F: 0, 5, 100, 400 mg/kg/day	NOAEL = 5 mg/kg/day LOAEL = 100 mg/kg/day based on decreased body weight gain, urinalysis parameters, and renal tubule changes. **No evidence of carcinogenicity**
870.4200 Carcinogenicity mice	44192602 (1996) Acceptable/guideline M & F: 0, 50, 100, 250, 500 mg/kg/day	NOAEL: Males: not identified; Females: 50 mg/kg/day LOAEL: Males: 50 mg/kg/day based on subscapular cataracts and decreased kidney tubular epithelium vacuolization. Females: 100 mg/kg/day based on renal tubular epithelial hyperplasia with dilatation. **No evidence of carcinogenicity**
870.5100 Bacterial reverse mutation assay (Ames test)	43441035 (1992) Unacceptable/guideline 0.05, 0.17, 0.5, 1.7, 5.0 µg/plate	Not tested at high enough concentrations to evaluate mutagenicity. Not mutagenic with and without S-9 activation at 5µg/plate and less.
870.5300 *In vitro* mammalian gene mutation assay	43441034 (1994) Acceptable/guideline 15.6 to 500 µg/ml (-S9), 7.81 to 500 µg/ml (+S9)	Negative with and without S-9 activation up to 500µg/ml.
870.5375 *In vitro* mammalian chromosome aberration (rat lymphocytes)	43441036 (1993) Acceptable/guideline 0, 17, 50, 170, 500 µg/ml (+S9 and -S9)	Negative with and without S-9 activation up to 500µg/ml.
870.5395 Mammalian erythrocyte micronucleus test	43441033 (1993) Acceptable/guideline 1250, 2500, 5000 mg/kg (oral gavage)	Negative at 24, 48, and 72 hour sacrifices..
870.6200 Acute neurotoxicity screening battery	44192601 (1996) Unacceptable/guideline 0, 200, 1000, 2000 mg/kg	NOAEL = 2000 mg/kg LOAEL = not defined
870.6300 Developmental neurotoxicity	NA	NA

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics	44103527 (1996) Acceptable/guideline 5, 500 mg/kg	Following an oral low dose, the apparent absorption (evidenced by renal excretion) was ~40% among male rats and ~65% among females. The compound was rapidly excreted in the urine and feces primarily as unchanged parent and a hydroxy-phenyl metabolite. At the higher dose, bioavailability was apparently decreased in both sexes with ≥81% of the dose eliminated into the feces with ~78% of the dose as unchanged parent. In both dose groups, sex-related differences were noted and included higher levels of renal excretion of parent by females, more extensive metabolism by males, and higher levels of residual label in the liver of males.
870.7600 Dermal penetration	NA	NA
Special studies:		
Chronic neurotoxicity screening battery	44103526 (1996) Unacceptable/nonguideline 0, 5, 100, 400 mg/kg/day	NOAEL = not defined LOAEL = not defined
Two-week dietary (rat)	43441030 (1992) Acceptable/nonguideline 0, 100, 500, 1000 mg/kg/day	NOAEL = 1000 mg/kg/day LOAEL = not identified
Two-week dietary (mouse)	43441028 (1993) Acceptable/nonguideline 0, 100, 500, 1000 mg/kg/day	NOAEL = 1000 mg/kg/day LOAEL = not identified

8.2 Summary of Toxicological Dose and Endpoints for Diclosulam for Use in Human Risk Assessment[1]

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment *to be completed later for risk assessment*	Study and Toxicological Effects
Acute Dietary females 13-50 years of age	NA	NA	There is no appropriate study with a single dose and end-point for this risk assessment.
Acute Dietary general population including infants and children	NA	NA	There is no appropriate study with a single dose and end-point for this risk assessment.
Chronic Dietary all populations	NOAEL= [5] mg/kg/day UF = [100] **Chronic RfD** = [0.05] mg/kg/day	FQPA SF = [deferred] **cPAD** = chronic RfD / FQPA SF = [deferred] mg/kg/day	[Chronic toxicity /oncogenicity- rat] LOAEL = [100] mg/kg/day based on [decreased body weight gain, urinalysis parameters, renal tubule changes]
Short-Term Dermal (1-7 days) (Occupational/ Residential)	NA Estimated absorption rate =6.5%	NA	There is no appropriate study with a single dose and end-point for this risk assessment.
Intermediate-Term Dermal (1 week - several months) (Occupational/ Residential)	NA	NA	There is no appropriate study with a single dose and end-point for this risk assessment.
Long-Term Dermal (several months - lifetime) (Occupational/ Residential)	NA	NA	There is no appropriate study with a single dose and end-point for this risk assessment.
Short-Term Inhalation (1-7 days) (Occupational/ Residential)	oral study NOAEL= [10] mg/kg/day (inhalation absorption rate = 100%)	**acceptable MOE** = [100] (Occupational) **acceptable MOE** = [deferred] (Residential, includes the FQPA SF)	[oral/developmental toxicity study-rabbit] Maternal and developmental LOAEL = [65] mg/kg/day based on [increased abortions, decreased fecal output, decreased maternal body weight gains and food consumption]

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment *to be completed later for risk assessment*	Study and Toxicological Effects
Intermediate-Term Inhalation (1 week - several months) (Occupational/ Residential)	oral study NOAEL= [10] mg/kg/day (inhalation absorption rate = 100%)	**acceptable MOE** = [100] (Occupational) **acceptable MOE** = [deferred] (Residential, includes the FQPA SF)	[oral/developmental toxicity study-rabbit] Maternal and developmental LOAEL = [65] mg/kg/day based on [increased abortions, decreased fecal output, decreased maternal body weight gains and food consumption]
Long-Term Inhalation (several months - lifetime) (Occupational/ Residential)	oral study NOAEL= [10] mg/kg/day (inhalation absorption rate = 100%)	**acceptable MOE** = [100] (Occupational) **acceptable MOE** = [deferred] (Residential, includes the FQPA SF)	[oral/developmental toxicity study-rabbit] Maternal and developmental LOAEL = [65] mg/kg/day based on [increased abortions, decreased fecal output, decreased maternal body weight gains and food consumption]
Cancer (oral, dermal, inhalation)	not likely human carcinogen	NA	No evidence of carcinogenic or mutagenic potential

[1] UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure

Attachment 2

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Date: February 2, 2000

Subject: **DICLOSULAM on PEANUTS and SOYBEANS.** Registration Toxicology Disciplinary Chapter.

DP Barcode: D249626; D258376; D262327
P.C. Code: 129122 Submission No.: S526363

To: William D. Wassell, Risk Assessor
RAB3/HED (7509C)

From: Ghazi A. Dannan, Ph.D., Pharmacologist Ghazi A. Dannan 2/2/2000
RAB3/HED (7509C)

Thru: Stephen C. Dapson, Ph.D., Branch Senior Scientist Stephen C. Dapson 02/03/2000
RAB3/HED (7509C)

I. ACTION REQUESTED

HED has been requested to review the toxicity data base for diclosulam (also known as XDE-564, XR-564, or XRD-564) to determine whether it supports a registration (62719-EII) and tolerances as an herbicide on peanuts and soybeans. The submitted MRIDs include 43441021-43441042, 43450401, 44103514, 44103522-44103527, 44192601, 44192602, 44207401, and 44207402. Also, the conclusions/recommendations of the HED HIARC and FQPA Safety Factor Committees are considered for this action.

II. CONCLUSIONS

In the "Toxicology Disciplinary Chapter for the Registration Support Document," HED has evaluated the toxicity data base and provided executive summaries of the DERs. The document also summarizes the selected hazard endpoints and recommendations that were made by the HIARC and FQPA Safety Factor Committees.

The toxicity data base does support the registration for diclosulam as an herbicide for use on peanuts and soybeans. All submitted studies were reviewed and all, except three, are considered acceptable. The Ames mutagenicity study (MRID 43441035) is a guideline study that was considered unacceptable because diclosulam was not tested at high enough concentrations to

assess mutagenicity. The remaining unacceptable studies are an acute and a chronic rat neurotoxicity studies and both are not required for this registration. The acute neurotoxicity study in rats (MRID 44192601) is considered unacceptable/guideline pending receipt of requested information. The rat chronic neurotoxicity study (MRID 44103526) is considered unacceptable/ nonguideline and may be upgradable; however, it will not satisfy the guideline for a subchronic neurotoxicity study.

The HIARC concluded that:

1) in accordance with the 1996 Cancer Risk Assessment Guidelines, diclosulam is a "**not likely human carcinogen**" based on the lack of evidence of carcinogenicity in mice or rats.

2) there is no indication of increased susceptibility of rats or rabbits to *in utero* and/or to post natal exposure to diclosulam.

3) a developmental neurotoxicity study in rats for diclosulam is **not recommended** based on the lack of evidence of neurotoxicity/neuropathology, no alterations in the fetal nervous system, and no increased susceptibility.

The FQPA Safety Factor Committee (SFC) evaluated the hazard and exposure data for diclosulam and recommended that the FQPA Safety Factor be removed (i.e reduced to 1x) in assessing the risk posed by this chemical. In its decision, the FQPA SFC relied on the HIARC's conclusions (items 2 and 3 above) and on the conclusion that the exposure assessment will not underestimate the potential dietary (food and water) exposures for infants and children resulting from the use of diclosulam (no residential exposure is expected).

Below is the Toxicology Disciplinary Chapter which was prepared by OakRidge and edited/ finalized by HED.

DICLOSULAM
PC Code: 129122

Toxicology Disciplinary Chapter for Registration Support Document

Date completed: December 1999

Contract Number: DW89938591-01

Prepared for:
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Arlington, VA 22202

Prepared by:
Chemical Hazard Evaluation Group
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Primary Reviewer:		
Cheryl B. Bast, Ph.D., D.A.B.T.	Signature:	Cheryl B Bast
	Date:	JAN 10 2000
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	Date:	JAN 10 2000
Robert H. Ross, M.S., Group Leader	Signature:	Robert H. Ross
	Date:	JAN 10 2000

Disclaimer

This data Summary may have been altered by the Health Effects Division subsequent to signing by Oak Ridge National Laboratory personnel.

Managed by Lockheed Martin Energy Research, Corp. for the U.S. Department of Energy under Contract No. DE-AC05-96OR22464.

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1.0 HAZARD CHARACTERIZATION

Diclosulam generally has low acute toxicity. The BF-564 (84.3% a.i.) appeared to be slightly more irritating to the skin and eye than XDE-564 (97.6% a.i.). Diclosulam is not a dermal sensitizer. Based on oral feeding studies, the primary target organs are the liver and kidney. In a subchronic rat feeding study, the primary target organ is the liver including increased organ weight, hepatocellular hypertrophy, and slight multifocal necrosis. Decreased body weight and kidney lesions were also noted. Liver effects were also noted in a subchronic dog study and included increased liver weight, centrilobular hepatocellular degeneration, and hepatocellular necrosis accompanied by elevated ALP, AST, and ALT. Other effects were decreased body weight, decreased food consumption, and renal changes in addition to hematological and clinical chemistry effects that were considered secondary to the debilitated condition of the animals. No significant treatment-related effects were noted in 21-day dermal studies in rabbits. In a developmental rat study, no treatment-related maternal or fetal effects were noted. However, in rabbits a dose-related increase in the number of abortions was observed. Prior to aborting, decreased fecal output, decreased food consumption, and decreased body weight gain were noted in does; the abortions may be secondary to these maternal effects. In a multigeneration rat reproductive study, no systemic toxicity to the parental animals was noted at the dose levels tested up to the limit dose. There were no treatment related findings in the reproductive system of parental animals of either sex. No systemic or developmental toxicity was noted in the offspring of either generation. In a chronic toxicity/oncogenicity study in the rat, the kidney is identified as a target organ. Changes in clinical chemistry and urinalysis parameters (indicative of altered renal tubule function) included increased creatinine, decreased urine specific gravity, increased urine volume, and decreased urinary protein concentration. Dose-related microscopic renal tubular pathology was also noted. Body weight gain was decreased 7-20% in treated animals compared to controls. No evidence of carcinogenicity was observed in rats or mice fed diclosulam, and there was no evidence of mutagenic activity. Diclosulam was classified as a "not likely human carcinogen." No evidence of neurotoxicity was observed, although neurotoxicity studies are considered inadequate.

2.0 REQUIREMENTS

The requirements (CFR 158.690) for Food/Feed Use for Diclosulam are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (Rodent)	yes	yes
870.3150	Oral Subchronic (Non-Rodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	no	-
870.3700a	Developmental Toxicity (Rodent)	yes	yes
870.3700b	Developmental Toxicity(Non-rodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (Rodent)	yes	yes[2]
870.4100b	Chronic Toxicity (Non-rodent)	yes	yes
870.4200a	Oncogenicity (Rat)	yes	yes[2]
870.4200b	Oncogenicity (Mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes[1]	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	no[3]
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (Hen)	no	-
870.6100b	90-Day Neurotoxicity Hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (Rat)	no	-
870.6200b	90 Day Neuro. Screening Battery (Rat)	no	-
870.6300	Develop. Neuro	no	-
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	-
Special Studies for Ocular Effects			
	Acute Oral (Rat)	no	-
	Subchronic Oral (Rat)	no	-
	Six-month Oral (Dog)	no	-

[1]can be used to satisfy 870.4100a (rodent chronic) and 870.4200a (rat oncogenicity)

[2]used to satisfy 870.4100a (rodent chronic) and 870.4200a (rat oncogenicity)

[3]study submitted but classified as unacceptable

3.0 DATA GAPS

The toxicological data base for diclosulam is adequate to support registration and tolerances. There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR 158. However, the Ames mutagenicity test has data gaps (highest dose tested not high enough). Also, both the acute neurotoxicity study (guideline) and the 1-year neurotoxicity study (non-guideline), both of which not required for this registration, are classified unacceptable pending the submission of additional information.

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of data base for acute toxicity: The data base for acute toxicity is considered complete. Studies were performed for both the technical (XDE-564, 97.6% a.i.) and for BF-309 (84.3% XDE-564). No additional studies are required at this time. Diclosulam generally has low acute toxicity. The BF-309 appeared to be slightly more irritating to the skin and eye than XDE-564. Diclosulam is not a dermal sensitizer. The acute toxicity data on diclosulam is summarized below in Table 2.

Table 2. Acute Toxicity Data on Diclosulam.

Guideline No./ Study Type	Test Substance*	MRID No.	Results	Toxicity Category
870.1100 Acute oral toxicity	XDE-564	43441021	LD_{50} >5000 mg/kg	IV
	BF-309	43441037	LD_{50} >5000 mg/kg	IV
870.1200 Acute dermal toxicity	XDE-564	43441022	LD_{50} >2000 mg/kg	III
	BF-309	43441038	LD_{50} >2000 mg/kg	III
870.1300 Acute inhalation toxicity	XDE-564	43441023	LC_{50} >5.04 mg/L	IV
	BF-309	43441039	LC_{50} >6.7 mg/L	IV
870.2400 Acute eye irritation	XDE-564	43441024	slight	IV
	BF-309	43441040	slight to moderate	III
870.2500 Acute dermal irritation	XDE-564	43441025	negative	IV
	BF-309	43441041	slight	IV
870.2600 Skin sensitization	XDE-564	43441026	negative	NA
	BF-309	43441042	negative	NA

*XDE-564 is diclosulam technical (97.6% a.i.). BF-309 contains 84.3% a.i.

4.2 Subchronic Toxicity

Adequacy of the data base for subchronic toxicity: The data base for subchronic toxicity is considered complete. No additional studies are required at this time. In a subchronic rat feeding study, the primary target organ is the liver. Liver effects included increased organ weight, hepatocellular hypertrophy, and slight multifocal necrosis. Kidney lesions were also observed in addition to decreased body weight which was considered secondary to decreased food consumption. Liver effects were also noted in a subchronic dog study and included increased liver weight, centrilobular hepatocellular degeneration, and hepatocellular necrosis accompanied by elevated ALP, AST, and ALT. There were also decreased body weight, food consumption, renal effects, and secondary clinical and hematological effects. No significant treatment-related effects were noted in the 21-day rabbit dermal studies using XDE-564 or BF-309.

870.3100 90-Day Oral Toxicity - Rat

In this 13-week study, Fischer 344 rats (10/sex/dose) were fed XDE-564 in diets formulated to yield 0, 50, 100, 500, or 1000 mg/kg/day. At the end of the main study, recovery was evaluated in randomly selected control and high-dose animals (10/sex/dose), which were fed basal diets for four additional weeks.

All animals survived to scheduled sacrifice without the appearance of any adverse or abnormal clinical signs.

Throughout the study, significant decreases in mean body weight were observed in 500 and 1000 mg/kg/day animals, with males being more adversely affected than females. At main study terminal sacrifice, male body weights were 19% lower than controls, and females, 12%. At 500 mg/kg/day, a 9% decrease was noted in males and an 8% decrease in females. At the end of the treatment-free recovery period, females recovered essentially all of the lost body weight, while males were 6% lower than control. The decreased body weights in males may be explained, in part, by decreased (13.4%, males; 7.5%,females) feed consumption. No clear effects were noted in feed efficiency, which was highly variable, especially in males.

Treatment-related effects included increased relative liver weights in males dosed at 100 mg/kg/day and higher and females at 500 and 1000 mg/kg/day. Histological examination of the livers revealed a dose-dependent increase in the incidence of hepatocellular hypertrophy in males (100, 500, 1000 mg/kg/day) and females (1000 mg/kg/day). Males also showed slight multifocal liver necrosis at 100 mg/kg/day and higher. Kidney lesions, noted in 500 and 1000 mg/kg/day males, consisted of decreased intracellular protein concentration in the proximal convoluted tubules; the study authors attributed this effect to decreased food consumption. None of these lesions was accompanied by alterations in clinical chemistry or hematology parameters.

Based on the results of this study, the NOEL for systemic toxicity was 50 mg/kg/day for

males and 100 mg/kg/day for females; the LOEL was 100 mg/kg/day for males (increased relative liver weight, hepatocellular hypertrophy, multifocal liver necrosis) and 500 mg/kg/day for females (decreased body weight, increased relative liver and brain weights).

CLASSIFICATION: CORE - Guideline

This study satisfied guideline [82-1(a)] requirements for a subchronic dietary toxicity study in the rat.

870.3150 90-Day Oral Toxicity - Dog

For 13 weeks, beagle dogs (4/sex/dose) were fed XDE-564 in diets formulated to yield 0, 5, 25, or 100/50 mg/kg/day. Because of health concerns and palatability problems at 100 mg/kg/day, the high-dose was reduced to 50 mg/kg/day on Day 50.

Treatment-related clinical signs were limited to high-dose females. One dog was found dead, without the appearance of any prior clinical signs. Two other females showed decreases in activity and severe muscle wasting; one of these females also had pale mucous membranes. All other animals survived to terminal sacrifice without the development of any treatment-related clinical signs.

Treatment-related toxicity included decreased mean body weight and food consumption in males and females treated at 100 mg/kg/day. After reduction of the dose to 50 mg/kg/day, all the male dogs and one female recovered and had positive body weight gains at terminal sacrifice. Two high-dose females were severely affected and had negative body weight gains at terminal sacrifice.

Hematology (decreased RBC, HGB and HCT) and clinical chemistry findings in high-dose females appeared to be secondary to the debilitated condition (emaciation, negative weight gains) of these animals.

Histopathological alterations were generally observed in mid- and high-dose males and females. Consistent with the elevations in ALP, AST, and ALT and increased relative liver weights, high-dose females also had hepatic lesions consisting of periportal aggregates of mononuclear cells, centrilobular hepatocellular degeneration, and individual hepatocellular necrosis. All mid- and high-dose males and mid-dose females showed centrilobular hepatocellular hypertrophy. Hemosiderin deposits were observed in the Kupffer cells of the mid- and high-dose males and low-, mid- and high-dose females. The kidneys of two high-dose females had perivascular aggregates of mononuclear cells in the cortex and lymphoplasmacytic inflammation in the pelvic region. For high-dose animals, granulocytic and megakaryocytic hyperplasia were present in the both the bone marrow of males and females and white pulp of the spleen of females.

The NOEL for systemic toxicity was 5 mg/kg/day; the LOEL for systemic toxicity was 25 mg/kg/day based on increased incidence of histopathological liver lesions.

CLASSIFICATION: CORE-Guideline; this study satisfies guideline [§82-1(b)] requirements for subchronic feeding study in dogs.

870.3200 21-Day Dermal Toxicity – Rabbit

A. XDE-564

In a 21-day repeated dose dermal toxicity study (MRID 44103523), groups of 5 male and 5 female New Zealand white rabbits were treated with XDE-564 (97.6%, Lot #151-86) moistened with distilled water at doses of 0, 100, 500, or 1000 mg/kg/day. Animals were treated by dermal occlusion for 6 hours/day, 5 days/week for 3 weeks.

No animals died during the study. There were no treatment-related clinical signs, dermal effects, effects on body weight, food consumption, hematology, clinical chemistry, ophthalmology, or organ weight. No gross or microscopic pathology were noted at necropsy.

The systemic and dermal NOAEL is the limit dose of 1000 mg/kg/day. A dermal and systemic LOAEL were not identified.

This study is classified as **Acceptable-Guideline** and does satisfy the requirements for a repeated-dose dermal study (82-2) in rabbits.

B. BF-309

In a 21-day repeated dose dermal toxicity study (MRID 44103514), groups of 5 male and 5 female New Zealand white rabbits were treated with BF-309 (83.1% a.i.) moistened with distilled water at doses of 0, 100, 500, or 1000 mg/kg/day. Animals were treated by dermal occlusion for 6 hours/day, 5 days/week for 3 weeks.

No animals died during the study. Very slight erythema was sporadically observed on treated animals, but the effect was not considered toxicologically significant. There were no treatment-related clinical signs, effects on body weight, food consumption, hematology, clinical chemistry, ophthalmology, or organ weight. No gross or microscopic pathology were noted at necropsy.

The systemic and dermal NOAEL is the limit dose of 1000 mg/kg/day. A dermal and systemic LOAEL were not identified.

This study is classified as **Acceptable-Guideline** and does satisfy the requirements for a repeated-dose dermal study (82-2) in rabbits.

Attachment 3

013847

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: **November 9, 1999**

MEMORANDUM

SUBJECT: ***DICLOSULAM*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Ghazi A. Dannan, Ph.D., Pharmacologist Ghazi A. Dannan 11/17/99
Registration Action Branch 3
Health Effects Division (7509C)

THROUGH: Stephen C. Dapson, Ph.D., Branch Senior Scientist
Registration Action Branch 3
Health Effects Division (7509C) Stephen C. Dapson 11/18/99
and
Jess Rowland, Co-Chairman 11/19/99
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: William Wassell, Risk Assessor
Registration Action Branch 3
Health Effects Division (7509C)

PC Code: 129122

On October 26, 1999, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of **Diclosulam**, established a Reference Dose (RfD) and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to Diclosulam as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were: David Anderson, William Burnam, Pamela Hurley, Mike Ioannou, Tina Levine (from RD), Susan Makris, Nancy McCarroll, Nicole Paquette, Jess Rowland (Co-Chairman), and P.V. Shah.

Member(s) in absentia were: Virginia Dobozy, Karen Hamernik, Kathleen Raffaele, Brenda Tarplee (Executive Secretary) and Pauline Wagner.

Data was presented by Ghazi Dannan of the Registration Action Branch 3.

Also in attendance were: Jack Arthur, Leung Cheng, Stephen Dapson, Clark Swentzel, and Bill Wassell (all from HED).

Data Presentation:
and
Report Presentation

Ghazi A. Dannan

Ghazi A. Dannan, Ph.D.
Pharmacologist

Report Concurrence:

Brenda Tarplee
Executive Secretary

I. INTRODUCTION

On October 26, 1999, the Health Effects Division (HED) Hazard Identification Assessment Review Committee evaluated the toxicology data base of **DICLOSULAM**, established a Reference Dose (RfD) and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to Diclosulam as required by the Food Quality Protection Act (FQPA) of 1996.

II. HAZARD IDENTIFICATION

A. Acute Reference Dose (RfD)

Study Selected: None.

MRID No.: N/A

Executive Summary: N/A

Dose and Endpoint for Establishing Oral RfD: N/A

Uncertainty Factor (UF): N/A

$$\textbf{Acute RfD} = \frac{\text{mg/kg}}{\text{(UF)}} = \textbf{mg/kg}$$

Comments about Study/Endpoint/Uncertainty Factor: There is no appropriate study with a single dose end-point for this risk assessment. In the rat acute neurotoxicity study, there was no compound-related effects on mortality, morbidity, clinical signs, body weight, FOB, motor activity, or neuropathology at any of the tested doses of 200, 1000, or 2000 mg/kg (MRID 44192601). In the rat developmental toxicity study, no treatment related effects were seen and the NOAEL/LOAEL for maternal or developmental toxicity were ≥1000/ >1000 mg/kg/day (MRID 43441032). In the rabbit developmental toxicity study, Diclosulam was administered at doses of 0, 10, 65, 325, and 650 mg/kg/day on GD 7-19; the maternal NOAEL/LOAEL were set at 10/65 mg/kg/day due to a dose-dependent increased abortions, and decreased maternal body weight gain, food consumption, and fecal output (MRID 44103524). The HIARC considered the dose-related increased abortions as an adverse fetal effect despite the fact that the abortions were probably related to maternal toxicity, the aborted fetuses were viable, and there was no increase in intra-uterine deaths (early or late resorptions). The developmental NOAEL/LOAEL were considered to be 10/65 mg/kg/day based on the dose-related increased abortions. There were no other treatment-related fetal or developmental effects on any of the examined parameters, including gravid uterine or fetal body weights, and gross, visceral, or skeletal

changes. However, because the abortions occurred late in the pregnancy (gestation days 21 to 27), the HIARC decided that this study is not appropriate for the acute exposure risk assessment.

This Risk Assessment is **NOT** required.

B. Chronic Reference Dose (RfD)

Study Selected: 2-Year Feeding Oncogenicity in Rats § 870.4300

MRID No.: 44103525

Executive Summary: In a combined chronic toxicity/oncogenicity study (MRID 44103525), XDE-564 (97.6% a.i.; Lot Number TSN 100168, DECO 151-86) was administered in the diet to 60 male and 60 female CDF®(F-344)CrlBR rats per group at doses of 0, 5, 100, or 400 mg/kg/day for up to slightly over 104 weeks except for 10 animals per sex per dose that were sacrificed at 52 weeks for interim evaluation and neurotoxicity assessment. The neurotoxicity results were reported separately (MRID 44103526) and will be evaluated in another DER.

Survival was unaffected by the treatment. Significant ($p<0.05$) treatment-related decreases in body weight and body weight gain were demonstrated in both sexes when fed XDE-564 at 100 and 400 mg/kg/day. Although the effects on total body weight did not approach a 10% reduction from control, the reduction in body weight gain was often in the range of 7–20% or more. Food consumption was similar in treated and control groups of both sexes, with the exception of the 400 mg/kg/day males, for which it was often from 5–10% lower.

There were slight (<5%) but statistically significant reductions ($p\leq 0.05$) in RBCs, hemoglobin, and hematocrit in both sexes at the high dose level. One such reduction was also observed in female rats of the 100 mg/kg/day group. The hematological effects observed are considered to be of no biological significance.

There were changes in several clinical chemistry and urinalysis parameters indicative of altered renal tubule function. Serum creatinine was increased (approximately 13%) in males in the 100 and 400 mg/kg/day groups and in females of the 400 mg/kg/day group at weeks 27, 52, 78 and/or 104. The mean urine specific gravity readings were slightly lower (although statistically significant) in the 100 and 400 mg/kg/day males and females at weeks 27, 52, 78 and/or 105. Other renal changes include increased urine volume and decreased urinary protein concentration in the mid- and high-dose groups of both sexes. These changes are considered to be a mild effect of the administration of XDE-564 on the kidney (mild tubular alterations). There were no findings of toxicological importance regarding gross pathology and organ weights.

A notable microscopic lesion in rats fed XDE-564 for 52 or 104 weeks was a subtle change in the kidneys which mostly affected the tubules of the corticomedullary region. The most salient feature of this renal alteration, with little or questionable toxicological significance, was a patchy to diffuse distribution change in the cytologic character and architecture of renal tubules, mostly within the corticomedullary junction. The incidence of tubular changes in the kidney was 4, 11, 41, and 77% in males and 4, 10, 69, and 82% in females in the 0, 5, 100 and 400 mg/kg/day groups, respectively. The corticomedullary tubular changes might well account for the altered renal tubule function. The incidence of hyperplasia of the pelvic epithelium was also dose-dependently increased among males and, compared to the control group (50%), this lesion was statistically significantly (≤ 0.05) increased in the mid- and high-dose male groups (72% and 85%, respectively).

No effects attributable to the test material and of biological or toxicological importance were observed at doses of 5 mg/kg/day.

The LOAEL is 100 mg/kg/day in both sexes based upon statistically significant decreases in body weight gain, increases in creatinine (males), decreases in urinary specific gravity and protein (both sexes), increased urine volume and renal tubule changes (both sexes) and increased incidence of pelvic epithelium hyperplasia (males). The absence of significant treatment-related effects identifies a NOAEL of 5 mg/kg/day in both sexes.

No evidence of carcinogenicity was observed in rats fed XDE-564 at doses of 5, 100, or 400 mg/kg/day for slightly over 104 weeks. Dosing was considered adequate because of the decreases in body-weight gain in both sexes fed 400 mg/kg/day.

This chronic/oncogenicity study in rats is classified as **Acceptable**/guideline and satisfies the guideline requirement for a combined chronic toxicity/oncogenicity study in rats (§83-5).

Dose and Endpoint for Establishing Chronic RfD: NOAEL 5 mg/kg/day based on decreased body weight gain and renal clinical and histopathological changes at 100 mg/kg/day.

Uncertainty Factor(s): 100 (10X for inter-species extrapolation and 10X for intra-species variability).

$$\textbf{Chronic RfD} = \frac{\text{5 mg/kg/day (NOAEL)}}{(100)} = \textbf{0.05 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor: The lowest NOAEL in the most sensitive species following chronic exposure.

This risk assessment is required.

C. Occupational/Residential Exposure

1. Dermal Absorption

Dermal Absorption Factor: 6.5% (Estimated)

There is no dermal absorption study with Diclosulam. However, the dermal absorption rate was estimated from the results of a 21-day dermal toxicity (MRID 44103523) and a developmental toxicity (MRID 44103524) studies in rabbits. In the developmental toxicity study, the maternal NOAEL/ LOAEL were 10/65 mg/kg/day based on a dose-related increased abortions, and decreased fecal output, maternal body weight gains, and food intake. In the 21-day rabbit dermal toxicity study there were no treatment-related clinical signs, or effects on body weight, food consumption, hematology, clinical chemistry, ophthalmology, or organ weights. The systemic and dermal NOAEL is the limit dose of 1000 mg/kg/day and LOAEL is unidentified. Assuming the dermal LOAEL is the limit dose of 1000 mg/kg/day, an approximate dermal absorption rate of 6.5% was derived by relating the ratio of the LOAELs from the oral and dermal studies (65/1000 x 100).

2. Short-Term Dermal (1-7 days)

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: N/A

Comments about Study/Endpoint: In a 21-day rabbit dermal toxicity study, there were no systemic toxicity at the limit dose of 1000 mg/kg/day (MRID 44103523).

This risk assessment is **NOT** required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: None

MRID No.: None

Executive Summary: None

Dose/Endpoint for Risk Assessment: N/A

Comments about Study/Endpoint: In a 21-day rabbit dermal toxicity study, there were no systemic toxicity at the limit dose of 1000 mg/kg/day (MRID 44103523).

This risk assessment is **NOT** required.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: N/A

Comments about Study/Endpoint: It is estimated that there will be one Diclosulam application per season. Therefore, the HIARC concluded that there is no long-term dermal exposure/risk potential.

This risk assessment is **NOT** required.

5. Inhalation Exposure (Any Time period)

There is no inhalation study available. However, based on the inhalation LC_{50}> 5.04 mg/L, Diclosulam is placed in Toxicity Category IV. Additionally, the use pattern (1 application/season) does not indicate a concern for potential long-term inhalation exposure. Nonetheless, the HIARC recommended that a route-to-route extrapolation should be made using the rabbit oral developmental study with the maternal/developmental NOAEL of 10 mg/kg/day based on the dose-dependent increased abortions, and decreased maternal body weight gain, food consumption, and fecal output (MRID 44103524). The following should be used:

> Convert the inhalation exposure component (i.e., μg a.i./day) using a 100% absorption rate (default value) and an application rate to an **equivalent oral dose** (mg/kg/day); this dose should then be compared to the oral NOAEL of 10 mg/kg/day to calculate the MOEs for short- and intermediate-terms.
>
> The use pattern doesn't indicate long-term inhalation risk potential.

D. Recommendation for Aggregate Exposure Risk Assessments

Aggregate exposure risk assessment will be limited to the chronic exposure (food + water) since doses and end-points were not identified for acute dietary or short-term and intermediate-term dermal or inhalation exposure risk assessments.

E. Margins of Exposures for Occupational/Residential Exposure Risk Assessments

An MOE of 100 is adequate for occupational exposure risk assessments. There are no residential uses.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

A. Combined Chronic Toxicity/Carcinogenicity Study in Rats § 870.4300

MRID No. 44103525

Discussion of Tumor Data: There was no evidence of carcinogenicity.

Adequacy of the Dose Levels Tested: The doses tested at 0, 5, 100, and 400 mg/kg/day were adequate for assessing carcinogenicity and chronic toxicity. The NOAEL was 5 mg/kg/day based mainly on statistically significant decreased body weight gain, and clinical, urinary, and renal histopathological changes indicative of effects on the kidney at the LOAEL of 100 mg/kg/day.

B. Carcinogenicity Study in Mice § 870.4200

MRID No. 44192602

Discussion of Tumor Data There was no treatment-related increase in tumor incidence compared to controls.

Adequacy of the Dose Levels Tested: The orally tested doses in both sexes were 0, 50, 100, 250, and 500 mg/kg/day. Body weight was decreased (by 3-6%) at several time points in mice of both sexes at the highest dose. There were dose-dependent increased subcapsular cataracts and decreased vacuolization of male kidney tubular epithelium. Also, there were statistically significant lower absolute and relative kidney weights in males at ≥100 mg/kg/day, and dose-dependent increased focal dilation/hyperplasia of the lining epithelium of kidney cortical tubules in females at doses ≥100 mg/kg/day.

C. Classification of Carcinogenic Potential In accordance with the 1996 Cancer Risk Assessment Guidelines, the HIARC classified Diclosulam as a "**not likely human carcinogen**" based on the lack of evidence of carcinogenicity in mice or rats.

IV. MUTAGENICITY

Results of the following four mutagenicity tests were negative. Three were guideline **acceptable** while data gaps were cited in the Ames mutagenicity study which was considered "**unacceptable.**"

A. Mouse Micronucleus Assay

MRID No.: 43441033
Executive Summary: Following oral administration of XDE-564 at doses of 1250, 2500 or 5000 mg/kg to CD-1 mice (5 animals/dose/sex/sacrifice time), bone marrow cells were collected 24, 48 and 72 hours after treatment and frequencies of micronucleated-polychromatic erythrocytes (PCEs) were determined. No significant increases in the frequency of micronucleated PCEs were noted in treated animals. The positive control (120 mg/kg, cyclophosphamide) had a significant increase in the frequency of micronucleated PCEs. The PCE-NCE ratios of treated and positive control animals were comparable to those of the negative control.

This study, with its negative findings, is classified as **Acceptable.** It satisfies the guideline requirements (§84-2) for an *in vivo* mammalian structural chromosomal assay.

B. CHO/HGPRT Forward Gene Mutation

MRID No.: 43441034
Executive Summary: XDE-564 was evaluated in two independent CHO/HGPRT forward gene mutation assays at 15.6 to 500 µg/ml (-S9) and 7.81 to 500 µg/ml (+S9). Under the conditions of this assay, XDE-564 did not show any mutagenic effects at the HGPRT locus with or without S9 metabolic activation. The high dose tested (500 µg/ml) was judged to be adequate since it was twice the solubility limit of XDE-564 in media.

This study satisfies the guideline (84-2) requirements for a "Structural chromosomal aberration test".

C. Ames/Reverse Mutation Assay

MRID No.: 43441035
Executive Summary: XR-564, at dose levels of 0.05, 0.17, 0.5, 1.7, and 5.0 μg/plate, was not mutagenic in the assay either with or without S-9 activation. From the results of the cytotoxicity assay, no reduction in background lawn was observed at a concentration of 500μg/plate. Therefore, the concentrations of XR-564 (5 μg/plate) were not adequately high enough to evaluate mutagenic potential.

Classification: Core - Unacceptable

This study does not satisfy the guideline (84-2) requirements for a "gene mutation" Assay.

D. Chromosomal Aberration Assay - Rat Lymphocytes

MRID No.: 43441036

Executive Summary: In two separate *in vitro* assays, rat lymphocytes were exposed for 4 hrs to XDE-564 ±S9 metabolic activation. In the first assay, cells scored for chromosomal aberrations were harvested 24 hrs after termination of exposure to 0, 50 and 500 µg/ml (cells exposed to 17 and 170 µg/ml had reduced mitotic indices and were not scored) -S9 and 0, 50, 170 or 500 µg/ml +S9. In the second assay, cells were scored following harvest at 24 hr after termination of exposure to 0, 50, 170 and 500 µg/ml ±S9. Cells were also scored following 48-hr harvest after termination of exposure to 0 and 500 µg/ml ±S9. In the first assay -S9, elevated (but not statistically significant) incidences of cells with chromosomal observations were observed at 50 and 170 µg/ml (means of 8 and 7.5%, compared with a mean of 3.5% for the solvent control), but this was not observed in the confirmatory assay -S9 (24 and 48 hr harvests) nor in either assay +S9. The positive controls gave appropriate responses. No consistent cytotoxicity to XDE-564 was observed; the highest concentration tested was 500 µg/ml since higher concentrations formed a precipitate in the test medium. Under the conditions of this assay, there is no evidence that XDE-564 causes chromosomal aberrations in rat lymphocytes.

Classification: Core - Acceptable

This study, with its negative results, satisfies the guideline [§84-2(b)] requirements for a "Structural chromosomal aberration test".

V. FQPA CONSIDERATIONS

A. Neurotoxicity

Acute Neurotoxicity -§81-8 (MRID # 44192601)

Following a single oral dose 0, 200, 1000, or 2000 (a limit dose) mg/kg, Fisher 344 rats (10/sex/group) were assessed daily for clinical observations and were evaluated for body weights, functional observational battery (FOB), motor activity and neuropathology. Cholinesterase inhibition was not evaluated. At study termination on day 16, 5 rats/sex/ group were perfused with glutaraldehyde/ paraformaldehyde, and histopathological evaluation of peripheral and central nervous system tissue was performed. There was no evidence of neuro-toxicological effects at any of the dose levels. Furthermore, there were no compound-related effects in mortality, morbidity, clinical signs, body weight, FOB, motor activity or neuropathology.

The LOAEL is not observed, based on lack of toxicity at any of the dose levels. The NOAEL is 2000 mg/kg for both sexes pending submission of requested information.

Subchronic Neurotoxicity- §82-7 (MRID 44103526)

There is no subchronic neurotoxicity study. However, after 1-year of compound administration (at 0, 5, 100, or 400 mg/kg/day) in the combined chronic/oncogenicity study, 12 rats/sex/group were subjected to FOB and locomotor activity tests in addition to neurohistopathological assessment (MRID 44103526). Clinical observations showed increased incidence of urine staining in females at 100 and 400 mg/kg/day dose levels and, to a lesser extent, in males at the high dose only. There was also a statistically significant decrease in hind limb grip strength in the mid-dose (week 39 only) and high-dose (weeks 26 and 39) males. No other treatment related signs of neurotoxicity were observed during the study. No neuropathological endpoints attributable to administration of the test material were observed during the histological examinations of the peripheral or central nervous systems of these animals at any exposure concentration; however, peripheral nervous system tissues were not processed according to Guideline procedures.

Due to study deficiencies (including lack of positive control data and insufficient procedural information), a NOAEL/LOAEL could not be determined for this study. Upon submission of requested additional information, NOAEL/LOAEL levels will be reassessed.

The urine staining effects and decreased hind-limb grip strength might not necessarily be due to neurotoxic effects. For instance, the staining could be attributed to the increased urine volumes (measured at weeks 78 and 105) and the mild kidney tubular alterations that were seen in the mid- and high dose groups of the main study (MRID 44103525). On the other hand, the decreased hind-limb grip strength could also be caused by a direct myotoxic effect on the tissue. However, several enzymes indicative of myotoxicity (but some of which are not specific to muscle injury), including creatine kinase, lactate dehydrogenase, SGOT and SGPT, were not increased in blood samples at weeks 27, 52, 78, and 105. Also, the increased plasma creatinine in the 2-year study, is not likely to be due to muscle catabolism but rather due to the mild kidney tubular alteration. Nonetheless, even if the decreased hind-limb grip strength is considered a neurotoxic effect, it is important to remember the following; the effect was seen after 26 and 52 weeks of compound administration at relatively high doses (100 and 400 mg/kg/day), there were no other findings that were indicative of neurotoxicity, and no grip strength effects were observed in the low dose group (5 mg/kg/day).

B. <u>Developmental Toxicity</u>

There is no evidence of increased fetal susceptibility in developmental oral toxicity studies in rats (MRID 43441032) and rabbits (MRID 44103524).

In the rat developmental toxicity study (MRID 43441032), groups of 30 bred Sprague-Dawley rats were administered daily gavage doses of Diclosulam at 0, 100, 500, and 1000 mg/kg/day during gestation days (GD) 6-15. There were no maternal or

developmental effects attributable to Diclosulam. The maternal and developmental NOAEL/LOAEL were ≥1000/>1000 mg/kg/day.

In a prenatal developmental toxicity study (MRID 44103524), groups of 40 (20 per each of phase 1 and phase 2) bred New Zealand rabbits were gavaged daily with Diclosulam at 0, 65, 325 and 650 mg/kg/day during GD 7-19. In phase 2 of the study, another group of 20 rabbits were administered Diclosulam at 10 mg/kg/day to ensure that the NOAEL is established. The maternal NOAEL/LOAEL were 10/65 mg/kg/day based on dose related increased abortions, and decreased maternal body weight gain, food consumption, and fecal output. The HIARC considered the dose-related increased abortions as an adverse fetal effect despite the fact that the abortions were probably related to maternal toxicity, the aborted fetuses were viable, and there was no increase in intra-uterine deaths (early or late resorptions). The HIARC determined that the developmental NOAEL/LOAEL should be 10/65 mg/kg/day based on the dose-related increased abortions. There were no other treatment-related fetal or developmental effects on any of the examined parameters, including gravid uterine or fetal body weights, and gross, visceral, or skeletal changes.

C. Reproductive Toxicity

In a multi-generation reproduction study (MRID 44207402), 30 CD rats/sex/group received 0, 50, 500, 750, or 1000 mg/kg/day Diclosulam in the diet for two-successive generations. No systemic toxicity to the parental animals was noted at the dose levels tested up to the limit dose. The Parental (Paternal/Maternal) Systemic Toxicity NOAEL/ LOAEL is ≥ 1000/> 1000 mg/kg/day. There were no systemic or developmental toxicity in the offspring of either generation even at the highest tested dose of 1000 mg/kg/day. The Offspring Systemic/ Developmental Toxicity NOAEL/LOAEL is ≥ 1000/ > 1000 mg/kg/day. There were no treatment related findings on the reproductive system/ parameters of animals of either sex. The Reproductive Toxicity NOAEL/LOAEL is ≥ 1000/ > 1000 mg/kg/day.

D. Additional information from the literature (IF AVAILABLE)

Not available.

E. Determination of Susceptibility

Based on the available data, there is no indication of increased susceptibility of rats or rabbits to *in utero* and/or to post natal exposure to Diclosulam. In the prenatal developmental toxicity studies, there was no apparent developmental toxicity in rats or rabbits at or below the maternal toxicity NOAEL values (*vide supra*). In the prenatal rabbit developmental toxicity study (MRID 44103524), there were dose-dependent increased late (GD 21-27) abortions at or above 65 mg/kg/day. As stated above, the

HIARC considered the dose-related increased abortions as an adverse fetal effect despite the fact that the abortions were probably related to maternal toxicity, the aborted fetuses were viable, and there was no increase in intra-uterine deaths (early or late resorptions). Both the maternal and developmental NOAEL/LOAEL were considered to be 10/65 mg/kg/day based on the dose-related increased abortions. There were other maternal effects, including decreased maternal body weight gain, food consumption, and fecal output; however, there were no other treatment-related fetal or developmental effects, including gravid uterine or fetal body weights, and gross, visceral, or skeletal changes. On the other hand, in the two-generation rat reproduction study, the parental and developmental/offspring systemic toxicity NOAEL/LOAEL were at or above the limit dose of 1000 mg/kg/day.

F. Recommendation for a Developmental Neurotoxicity Study

Based on the lack of evidence of neurotoxicity/neuropathology and no alterations in the fetal nervous system as well as no increased susceptibility, the HIARC **did not recommend** a developmental neurotoxicity study in rats for Diclosulam.

G. Hazard-Based Recommendation of the FQPA Safety Factor

The HIARC, based on hazard assessment, recommends to the FQPA Safety Committee that the additional 10x factor should be removed because:

(i) Developmental toxicity studies showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.

(ii) A two-generation reproduction toxicity study in rats showed no increased susceptibility in pups when compared to adults.

(iii) There was no evidence of abnormalities in the development of fetal nervous system in the pre/post natal studies. Neither brain weight nor histopathology of the nervous system was affected in the subchronic and chronic toxicity studies.

(iv) The toxicology data base is complete and there are no data gaps. There is no evidence to require a developmental neurotoxicity study.

The final recommendation on the FQPA Safety Factor, however, will be made during risk characterization by the FQPA Safety Committee.

VI. HAZARD CHARACTERIZATION

There are no gaps in the data base and the scientific quality of the available studies is acceptable. There are Guideline acute and subchronic neurotoxicity studies as well as developmental oral toxicity studies in rats and rabbits and a multi-generation reproduction study in rats. The developmental and reproduction studies showed no effect on reproduction and no increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to Diclosulam as demonstrated by equal or higher LOAEL values than those needed to produce maternal toxicity. Also, there were no reported neurobehavioral or neuropathological effects in any of the guideline studies including the acute neurotoxicity study and the non-guideline 1-year neurotoxicity study. There were no evidence for carcinogenicity in male and female rats and mice. Also, all four mutagenicity tests were negative with three being guideline **acceptable** while the Ames mutagenicity study had data gaps and was considered "**unacceptable.**" The HIARC considered the carcinogenic potential of Diclosulam as a **"Not Likely"**.

On the other hand, among the common toxicological findings were renal function and kidney changes in both the rat and mouse chronic toxicity feeding studies (MRID 44103525 and 44192602), while in the rat and dog subchronic studies (MRID 43441029 and 43450401) the liver seemed to be a target organ, including increased relative liver weight and histopathological liver lesions.

The HIARC, concluded that the data base and findings were adequate to rule out, with reasonable certainty, possible increased susceptibility of infants and children to Diclosulam and, therefore, the HIARC decided not to recommend a developmental neurotoxicity study.

VII. DATA GAPS

There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158. However, the Ames mutagenicity test has data gaps (highest dose tested not high enough) and both the acute neurotoxicity study (guideline) and the 1-year neurotoxicity study (non-guideline) are classified unacceptable pending the submission of additional information.

VIII. ACUTE TOXICITY

Acute Toxicity of Diclosulam

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral - Rat	43441021	LD_{50} > 5000 mg/kg	IV
81-2	Acute Dermal - Rabbit	43441022	LD_{50} > 2000 mg/kg	III
81-3	Acute Inhalation - Rats	43441023	LC_{50} > 5.04 mg/L	IV
81-4	Primary Eye Irritation - Rabbit	43441024	Slight	IV
81-5	Primary Skin Irritation - Rabbit	43441025	Negative	IV
81-6	Dermal Sensitization - Guinea Pig	43441026	Negative	

IX. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary		This risk assessment is not required. There is no *appropriate study with a single dose and end-point for* this risk assessment.	
	Acute RfD = Not Required		
Chronic Dietary	NOAEL = 5 UF = 100	Decreased body weight gain, changes in renal tubule and kidney function parameters, and increased incidence of male kidney pelvic epithelium hyperplasia.	Chronic Toxicity/ Oncogenicity-Rat
		Chronic RfD = 0.05 mg/kg/day	
Short- and Intermediate-Term (Dermal)	NOAEL ≥1000	This risk assessment is not required. In a 21-day rabbit dermal toxicity study, no systemic toxicity was observed at the limit dose (1000 mg/kg/day).	
Long-Term (Dermal)		This risk assessment is not required. Based on the use pattern (1 application/year), there is no potential long-term dermal exposure/risk.	
Short- and Intermediate-Term (Inhalation)	NOAEL= 10	Increased abortions and decreased maternal body weight gain, food consumption, and fecal output.	Developmental Toxicity-Rabbit
Long Term (Inhalation)		This risk assessment is not required. Based on the use pattern (1 application/year), there is no potential long-term inhalation exposure/risk.	

Attachment 4

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

013875

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

December 3, 1999

MEMORANDUM

SUBJECT: *DICLOSULAM* - Report of the FQPA Safety Factor Committee

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: William Wassell, Risk Assessor
Registration Action Branch 3
Health Effects Division (7509C)

PC Code: 129122

The FQPA Safety Factor Committee met on November 15, 1999 to evaluate the hazard and exposure data for diclosulam and recommended that the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996) be removed (1x) in assessing the risk posed by this chemical.

I. HAZARD ASSESSMENT

(*Memorandum:* G. Dannan to E. Zager dated November 3, 1999)

A. Adequacy of the Toxicology Database

The toxicology database for Diclosulam is complete and there are no data gaps. The HED Hazard Identification Assessment Review Committee (HIARC) concluded that a developmental neurotoxicity study was not required.

B. Determination of Susceptibility

Based on the available studies, there is no expected susceptibility concern for infants and children. There is no evidence of increased fetal and/or offspring susceptibility in the developmental oral toxicity studies in rats and rabbits; or in the multi-generation rat reproduction study.

II. EXPOSURE ASSESSMENTS

A. Dietary (Food) Exposure Considerations

(*Correspondence:* L. Cheng to B. Tarplee dated November 3, 1999.)

Diclosulam is a new herbicide for which tolerances are proposed on peanuts and soybeans. Tolerances will be established in terms of the parent compound only. Livestock metabolism data and the theoretical maximum livestock dietary burdens indicate that tolerances for meat, milk, poultry, and eggs are not required. There are no Codex MRLs.

The HED Metabolism Assessment Review Committee (MARC) concluded that only the parent compound should be included in the tolerance expression and considered in dietary (food) risk assessments for diclosulam. The MARC also recommended that the registrant provide confirmatory data on the level of the 2,6-DCA metabolite in peanuts and soybeans (DRAFT Memorandum: L. Cheng to G. Kramer, dated October 27, 1999).

No monitoring data are available for this new chemical. However, crop field trial data are available and indicate that levels of diclosulam are below 0.01 ppm in peanuts and soybeans following the proposed use. The registrant has provided % market share estimates for peanuts and soybeans. This information will need to be validated by the Biological and Economical Analysis Branch (BEAD).

The HED Dietary Exposure Evaluation Model (DEEM) will be used to assess the risk from chronic dietary exposure to residues of diclosulam in food (acute assessment is not required). At the time of this meeting, the analysis was not complete. Since there are no monitoring data or Agency percent crop treated (%CT) information, it is expected that this analysis will be unrefined (Tier 1) resulting in an overestimate of the dietary (food) exposure resulting from the use of diclosulam.

The Committee recognizes that further refinement to the dietary food exposure analyses may be required as the risk assessment is developed. Therefore, provided the final dietary food exposure assessment does not underestimate the potential risk for infants and children, the safety factor recommendations of this Committee stand.

B. Dietary (Drinking Water) Exposure Considerations

(*Correspondence:* A. Chiri to B. Tarplee and J. Holmes dated October 13, 1999)

The environmental fate database for diclosulam is adequate for the characterization of drinking water exposure. The data indicate that this chemical is moderately persistent and mobile. Fate data for the three degradation products, 5-OH XDE-564, 5-oxo XDE-564, and ASTP indicate that these compounds are also potentially mobile (assessment of the environmental persistence of the metabolites is currently under review). In an *ad hoc* meeting of the HED MARC, it was concluded that only the parent compound be considered in dietary (drinking water) risk assessment for diclosulam. The MARC also recommended that the registrant should provide levels of 2,6-DCA in drinking water in the future (*Correspondence:* L. Cheng to B. Tarplee dated December 3, 1999.).

No monitoring data are available for diclosulam. Estimated Environmental Concentrations (EECs) for surface and ground water have been calculated based on the Tier I models GENEEC and SCIGROW, respectively, using the application scenario (use rate, etc.) for soybeans. When appropriate, other Tier II models will be used to refine the water exposure assessment.

C. Non-Occupational (Residential) Exposure Considerations

(*Correspondence:* J. Arthur to B. Tarplee dated November 4, 1999.)

There are no registered residential uses for diclosulam, therefore non-occupational exposure is not expected.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

A. Recommendation of the Factor

The Committee recommended that the FQPA safety factor for protection of infants and children (as required by FQPA) be **removed (1x).**

B. Rationale for Removing the FQPA Safety Factor

The Committee concluded that the safety factor could be removed because:

1. The toxicology database is complete for the assessment of the effects following *in utero* and/or postnatal exposure to diclosulam;

2. the toxicity data provided no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure;

3. a developmental neurotoxicity study is not required by HIARC; and

4. the exposure assessment approach will not underestimate the potential dietary (food and water) exposures for infants and children resulting from the use of diclosulam (no residential exposure is expected).

FQPA SAFETY FACTOR COMMITTEE MEETING

15NOV1999

DICLOSULAM

Name	Division/Branch
Jess Rowland	HED/RRB3
Ray West	HED/RRB4
Susan Makris	HED/RRB4
Angel Chiri	EFED/ERB4
Leung Cheng	HED/RAB3
Clark Swentzel	HED/RAB3
Luis Suguiyama	RD/FB
Carl Scrable	RD/FB
Linda Kutney	RD/FB
Kathy Monk	SRRD
Bill Wassell	HED/RAB3
Debbie McCall	RD
Jean Holmes	EFED/ERB2
Ghazi Dannan	HED/RAB3
Edward Zager	HED
Ty	HED/SAB

Attachment 5

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

December 22, 1999

MEMORANDUM

SUBJECT: PP#6F4784 & PP#7F4856. Chronic Dietary Exposure Analysis for Diclosulam (XDE-564) on Peanut and Soybean. PC Code 129122. DP Barcode: D261875.

FROM: Leung Cheng, Chemist Lee Cheng
Registration Action Branch 3
Health Effects Division (7509C)

THROUGH: Stephen Dapson, Branch Senior Scientist Stephen C. Dapson 12/22/99
Registration Action Branch 3
Health Effects Division (7509C)

TO: William Wassell, Risk Assessor
Registration Action Branch 3
Health Effects Division (7509C)

Action Requested

Provide a chronic dietary exposure analysis for the proposed Section 3 use of diclosulam on peanut and soybean. RAB3 has recommended a conditional registration in that tolerances be established at 0.02 ppm on peanut nutmeat and soybean seed as a result of the proposed use.

Executive Summary

The chronic dietary analysis for diclosulam is a conservative assessment (Tier 1) using tolerance level residues for peanut and soybean, and assuming that 100 percent of the commodity has been treated with diclosulam. Exposure estimates are below HED's level of concern for the general U.S. population and all population subgroups.

Toxicology Information

The Hazard Identification Assessment Review Committee (HIARC) met on 10/26/99 and selected appropriate doses and endpoints for diclosulam. There is no appropriate study with a single dose and end-point for acute risk assessment, therefore, an acute assessment is not required. The doses and toxicological endpoints selected for dietary exposure scenarios are summarized in Table 1 (HIARC report, G. Dannan, 11/9/99).

For this Section 3 use, the 10x FQPA safety factor is removed. Therefore, the chronic population adjusted dose (cPAD) is the same as the chronic RfD, 0.05 mg/kg/day (FQPA report, B. Tarplee, 12/3/99).

Table 1. Reference Dose and Endpoint Selection

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary		This risk assessment is not required. There is no appropriate study with a single dose and end-point for this risk assessment.	
	Acute RfD = Not Required		
Chronic Dietary	NOAEL = 5 UF = 100	Decreased body weight gain, changes in renal tubule and kidney function parameters, and increased incidence of male kidney pelvic epithelium hyperplasia.	Chronic Toxicity/ Oncogenicity-Rat
		Chronic RfD = 0.05 mg/kg/day **cPAD = 0.05 mg/kg/day**	

No evidence of carcinogenicity was found; therefore, cancer assessment is not required.

Residue Information

Since this is a first crop use, the recommended tolerances for peanut and soybean of 0.02 ppm are used for chronic exposure analysis. No established tolerances exist for diclosulam. Default concentration factors were used for the processed commodities.

Consumption Data and Dietary Risk Analysis

HED is currently using software developed by Novigen Sciences, Inc. (DEEM™) to calculate acute and chronic dietary risk estimates for the general U.S. population and various population subgroups. The food consumption data used in the program are taken from the USDA Continuing Survey of Food Intake by Individuals (CSFII). The Agency is currently using

1989-92 consumption data within version 6.77 of DEEM™. Consumption data are averaged for the entire U.S. population, and within population subgroups such as "all infants" to support chronic risk assessment, but retained as individual daily consumption data points to support acute risk assessment (which is based on distributions of consumption estimates for either deterministic- or probabilistic-type exposure estimates). The DEEM™ software is capable of calculating probabilistic type risk assessments when appropriate residue data (distribution of residues) are available.

For chronic risk assessments, residue estimates for foods (e.g. apples) or food-forms (e.g. apple juice) of interest are multiplied by the averaged consumption estimate of each food/food-form of each population subgroup. Exposure estimates are expressed in mg/kg bw/d and as a percent of the cPAD.

Results

A summary of the residue information used in the chronic exposure analysis is attached (Attachment 2). The chronic analysis for the U.S. population and other subgroups are presented in Table 2. Exposure extimates are well below HED's level of concern for the general U.S. population and all population subgroups.

Table 2. Chronic Dietary Exposure Estimates

Population subgroup	Exposure, mg/kg/day	%cPAD
US population	0.000011	<1
All infants	0.000047	<1
Children 1-6 yrs	0.000024	<1
Children 7-12 yrs	0.000016	<1
Females 13+ (preg/not nursing)	0.000007	<1
Females 13+ (nursing)	0.000010	<1
Males 13-19 yrs	0.000012	<1
Males 20+ yrs	0.000008	<1

Conclusion

The Tier 1 chronic dietary analysis is highly conservative using of the recommended tolerance level residue values and assuming that 100 percent of the peanut and soybean were treated. The percent cPAD is below HED's level of concern for the U.S. population and all population subgroups.

Attachments -
1. Chronic Exposure Analysis
2. Values for Chronic Analysis

cc:RAB3 Reading F,6F4784, 7F4856, L. Richardson (DRES), Cheng
RD/I:DESAC(JRowell&CChristensen):12/17/99:SDapson:12/21/99
7509C:RAB3:LCheng:CM#2:RM810A:12/15/99:3rab\diclosulam.dmr

Attachment 1

U.S. Environmental Protection Agency Ver. 6.76
DEEM Chronic analysis for DICLOSULAM (1989-92 data)
Residue file name: C:\deem\diclosulam.R96 Adjustment factor #2 NOT used.
Analysis Date 12-06-1999/15:40:13 Residue file dated: 12-06-1999/15:39:19/8
Reference dose (RfD, CHRONIC) = .05 mg/kg bw/day
COMMENT 1: fqpa=1x; cPAD=cRfD

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of Rfd
U.S. Population (total)	0.000011	0.0%
U.S. Population (spring season)	0.000010	0.0%
U.S. Population (summer season)	0.000011	0.0%
U.S. Population (autumn season)	0.000011	0.0%
U.S. Population (winter season)	0.000011	0.0%
Northeast region	0.000011	0.0%
Midwest region	0.000011	0.0%
Southern region	0.000010	0.0%
Western region	0.000010	0.0%
Hispanics	0.000009	0.0%
Non-hispanic whites	0.000011	0.0%
Non-hispanic blacks	0.000010	0.0%
Non-hisp/non-white/non-black)	0.000009	0.0%
All infants (< 1 year)	0.000047	0.1%
Nursing infants	0.000012	0.0%
Non-nursing infants	0.000061	0.1%
Children 1-6 yrs	0.000024	0.0%
Children 7-12 yrs	0.000016	0.0%
Females 13-19(not preg or nursing)	0.000009	0.0%
Females 20+ (not preg or nursing)	0.000007	0.0%
Females 13-50 yrs	0.000008	0.0%
Females 13+ (preg/not nursing)	0.000007	0.0%
Females 13+ (nursing)	0.000010	0.0%
Males 13-19 yrs	0.000012	0.0%
Males 20+ yrs	0.000008	0.0%
Seniors 55+	0.000006	0.0%
Pacific Region	0.000010	0.0%

Attachment 2

```
"diclosulam"
 0.05
NEWN,          0
NOEL,          5             0             0
12-06-1999/15:39:19
-1  "fqpa=1x; cPAD=cRfD"
 999
 255  15029AA,6A,  0.02      0.33       1          0   "Soybeans-sprouted seeds", ""
 293  27007OA,O,   0.02      1          1          0   "Peanuts-oil", ""
 297  27010OA,6A,  0.02      1          1          0   "Soybeans-oil", ""
 303  15023AA,6A,  0.02      1          1          0   "Soybean-other", ""
 304  28023AB,6A,  0.02      1          1          0   "Soybeans-mature seeds dry", ""
 305  28023WA,6A,  0.02      1          1          0   "Soybeans-flour (full fat)", ""
 306  28023WB,6A,  0.02      1          1          0   "Soybeans-flour (low fat)", ""
 307  28023WC,6A,  0.02      1          1          0   "Soybeans-flour (defatted)", ""
 403  15006BT,O,   0.02      1.89       1          0   "Peanuts-butter", ""
 482  No Code,O,   0.02      1          1          0   "Soybeans-protein isolate", ""
 940  No Code,O,   0.02      1          1          0   "Peanuts-hulled", ""
```

Attachment 6

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

PC Code: 129122
DP Barcode: D260980

Date: November 10, 1999

MEMORANDUM

SUBJECT: Tier I Estimated Environmental Concentrations for Diclosulam on Soybeans

TO: Donald Stubbs, Chief
Herbicide Branch
Registration Division

FROM: Rudy A. Pisigan, Jr., Ph.D., Environmental Chemist
Ronald Parker, Ph.D., Environmental Engineer
Environmental Risk Branch IV
Environmental Fate and Effects Division

THROUGH: Mah T. Shamim, Ph.D., Chief
Environmental Risk Branch IV
Environmental Fate and Effects Division

SUMMARY

This memo presents the Tier I Estimated Environmental Concentrations (EECs) for the herbicide diclosulam (label or trade name: Strongman*) calculated using GENEEC (surface water) and SCIGROW (groundwater) for use in the human health risk assessment. The EECs were calculated using the maximum application rate of 0.0315 lb a.i./ acre through ground spray treatment. For surface water, the acute (peak) value is 1.54 ppb and the chronic (average 56-day) value is 1.28 ppb. The groundwater screening concentration is 0.035 ppb. These values represent upper-bound estimates of the concentrations that might be found in surface water and groundwater due to the use of diclosulam on soybeans.

Should the results of this assessment indicate a need for further refinement, please contact us as soon as possible so that we may schedule a Tier II assessment.

Background Information on GENEEC:

GENEEC is a screening model designed to estimate the pesticide concentrations found in water for use in ecological risk assessments. As such, it provides high-end values on the concentrations that might be found in ecologically sensitive environments due to the use of a pesticide. GENEEC is a single-event model (one runoff event), but can account for spray drift from multiple applications. GENEEC is hardwired to represent a 10-ha field immediately adjacent to a 1-ha pond, 2 meters deep with no outlet. The pond receives a spray drift event from each application plus one runoff event. The runoff event moves a maximum of 10% of the applied pesticide into the pond. This amount can be reduced due to degradation on field and the effects of binding to soil. Spray drift is equal to 1% of the applied concentration from the ground spray application and 5% for aerial application.

Though GENEEC was not originally designed for use in drinking water risk assessments, it does provide a reasonable upper-bound estimate for screening purposes. Surface-water-source drinking water tends to come from bodies of water that are substantially larger than a 1-ha pond. Furthermore, GENEEC assumes that essentially the entire basin receives an application of the chemical. In virtually all cases, basins large enough to support a drinking water utility will contain a substantial fraction of area that does not receive the chemical. Additionally, there is always some flow (in a river) or turnover (in a lake or reservoir) of the water so that the persistence of the chemicals near the drinking water utility intakes will be overestimated. Given all these factors, GENEEC does provide an upper-bound estimate of the concentration of a pesticide that could be found at the drinking water utility and therefore can be appropriately used in screening calculations. If a risk assessment performed using GENEEC output does not exceed the level of concern, then one can be reasonably confident that the actual risk will not be exceeded. However, because GENEEC can substantially overestimate true drinking water concentrations, it will be necessary to refine the GENEEC estimates if the level of concern is exceeded.

Background Information on SCIGROW:

SCIGROW provides a groundwater screening exposure value to be used in determining the potential risk to human health from drinking water contaminated with the pesticide. Since the SCIGROW concentrations are likely to be approached in only a very small percentage of drinking water sources, i.e., highly vulnerable aquifers, it is not appropriate to use SCIGROW concentrations for national or regional exposure estimates.

SCIGROW estimates likely groundwater concentrations if the pesticide is used at the maximum allowable rate in areas where groundwater is exceptionally vulnerable to contamination. In most cases, a large majority of the use area will have groundwater that is less vulnerable to contamination that the areas used to derive the SCIGROW estimate.

Modeling Inputs and Results:

Table 1 and Table 2 summarize the input values used in the model runs for GENEEC and SCIGROW, respectively. The lowest Koc out of the 4 reported values was used in GENEEC. The Koc value of the alkaline soil was used in SCIGROW after considering the ionizable behavior of diclosulam (Barrett, M. 1999. Personal Communication). The aerobic soil metabolism half-life and other fate parameters were taken the study submitted by the registrant and the review of Jones, A.W., 1995 [Status of Environmental Fate Data Requirements for XDE-564 (Diclosulam)] The modeling results associated with maximum allowable rate per year (0.0315 lbs ai/acre) of diclosulam for soybeans are presented in Table 3. Attached to this memo are Attachment 1 and Attachment 2 of the original printouts generated from the GENEEC and SCIGROW model runs, respectively.

Table 1. Environmental Fate Input Parameters for GENEEC..

Water Solubility (Distilled water, 20 ^{0}C)	100 mg/L
Hydrolysis Half Life (pH 7)	stable
Aerobic Soil Metabolism Half Life	54 days
Aerobic Aquatic Metabolism Half Life	107 days
Photolysis Half Life	119 days
Organic Carbon Adsorption Coefficient (Koc)	33 mL / g o.c.

Table 2. Environmental Fate Input Parameters for SCIGROW.

Herbicide	Diclosulam
Organic Carbon Partition Coefficient (Koc)	55 mL / g o.c.
Aerobic Soil Metabolism Half-Life	54 days
Date	November 10, 1999

Table 3. Application Information and Modeling Results for Use of Diclosulam on Soybeans

Application Method	Ground Spray
Application Rate	0.0315 lbs a.i/acre
Application Frequency	1 / Year
Incorporation Depth	1 inch
Application Interval (days)	not applicable
GENEEC Peak EEC	**1.54 ppb**
GENEEC 56-Day EEC	**1.28 ppb**
SCIGROW Groundwater Concentration	**0.035 ppb**

ATTACHMENT 1 - GENEEC PRINTOUT

RUN No. 1 FOR **DICLOSULAM** INPUT VALUES

RATE (#/AC) ONE(MULT)	APPLICATIONS NO.-INTERVAL	SOIL KOC	SOLUBILITY (PPM)	% SPRAY DRIFT	INCORP DEPTH(IN)
0.032(0.032)	1 1	33.0	100.0	1.0	1.0

FIELD AND STANDARD POND HALFLIFE VALUES (DAYS)

METABOLIC (FIELD)	DAYS UNTIL RAIN/RUNOFF	HYDROLYSIS (POND)	PHOTOLYSIS (POND-EFF)	METABOLIC (POND)	COMBINED (POND)
54.00	2	N/A	120.00-14724.00	107.00	106.23

GENERIC EECs (IN PPB)

PEAK GEEC	AVERAGE 4 DAY GEEC	AVERAGE 21 DAY GEEC	AVERAGE 56 DAY GEEC
1.54	1.52	1.44	1.28

ATTACHMENT 2 - SCIGROW PRINOUT

RUN No. 1 FOR **DICLOSULAM** INPUT VALUES

APPL (#/AC) RATE	APPL. NO.	URATE (#/AC/YR)	SOIL KOC	SOIL AEROBIC METABOLISM (DAYS)
.032	1	.032	55.0	54.0

GROUND-WATER SCREENING CONCENTRATIONS IN PPB

.035325

A= 49.000 B= 60.000 C= 1.690 D= 1.778 RILP= 3.755
F= .050 G= 1.121 URATE= .032 GWSC= .035325

Attachment 7

(Base label):

(logo) DowElanco

Strongarm*

For Broadleaf Weed Control in Soybeans and Peanuts

Active Ingredients:

diclosulam: N-(2,6-dichlorophenyl)-5-ethoxy-7-fluoro[1,2,4]triazolo-[1,5-c]pyrimidine-2-sulfonamide	84%
Inert Ingredients	16%
Total	100%

Contains 0.84 pounds of active ingredient per pound of product.

U.S. Patent No. 5,163,995

Keep Out of Reach of Children

CAUTION PRECAUCION

Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle. (If you do not understand the label, find someone to explain it to you in detail.)

Precautionary Statements

Hazards to Humans and Domestic Animals

Causes Eye Irritation • Harmful If Absorbed Through Skin

Avoid contact with eyes, skin, or clothing. Wash thoroughly with soap and water after handling.

Personal Protective Equipment (PPE)

Applicators and other handlers must wear:

- Long-sleeved shirt and long pants
- Waterproof gloves
- Shoes plus socks

Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry.

User Safety Recommendations

Users should:

- Wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet.

First Aid

If in eyes: Flush with plenty of water. Get medical attention if irritation persists.

If on skin: Wash with plenty of soap and water. Get medical attention if irritation persists.

Environmental Hazards

Do not apply directly to water, to areas where surface water is present, or to intertidal areas below the mean high water mark. Do not contaminate water by cleaning of equipment or when disposing of equipment washwaters.

Agricultural Use Requirements

Use this product only in accordance with its labeling and with the Worker Protection Standard, 40 CFR part 170. Refer to label booklet under "Agricultural Use Requirements" in the Directions for Use section for information about this standard.

Refer to label booklet for additional precautionary information including Personal Protective Equipment (PPE), User Safety Recommendations and Directions for Use including Storage and Disposal.

Notice: Read the entire label. Use only according to label directions. **Before buying or using this product, read "Warranty Disclaimer" and "Limitation of Remedies" inside label booklet.**

In case of emergency endangering health or the environment involving this product, call collect 517-636-4400.
Agricultural Chemical: Do not ship or store with food, feeds, drugs or clothing.

EPA Reg. No. 62719-XXX

EPA Est. 00000-XX-00

*Trademark of DowElanco
DowElanco • Indianapolis, IN 46268 U.S.A.

Herbicide

Net Wt_____lbs.

(Label Booklet cover):

(logo) DowElanco

Strongarm*

For Broadleaf Weed Control in Soybeans and Peanuts

Active Ingredients:

diclosulam: N-(2,6-dichlorophenyl)-5-ethoxy-7-fluoro[1,2,4]triazolo-[1,5-c]pyrimidine-2-sulfonamide	84%
Inert Ingredients	16%
Total	100%

Contains 0.84 pounds of active ingredient per pound of product.

U.S. Patent No. 5,163,995

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EPA Reg. No. 62719-XXX

EPA Est. 00000-XX-00

*Trademark of DowElanco

DowElanco • Indianapolis, IN 46268 U.S.A.

Herbicide

Net Wt_____lbs.

(Page 1 through end):

Precautionary Statements

Hazards to Humans and Domestic Animals

Causes Eye Irritation • Harmful If Absorbed Through Skin

Avoid contact with eyes, skin, or clothing. Wash thoroughly with soap and water after handling.

Personal Protective Equipment (PPE)

Applicators and other handlers must wear:
- Long-sleeved shirt and long pants
- Waterproof gloves
- Shoes plus socks

Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry.

User Safety Recommendations

Users should:
- Wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet.

First Aid

If in eyes: Flush with plenty of water. Get medical attention if irritation persists.
If on skin: Wash with plenty of soap and water. Get medical attention if irritation persists.

Environmental Hazards

Do not apply directly to water, to areas where surface water is present, or to intertidal areas below the mean high water mark. Do not contaminate water by cleaning of equipment or when disposing of equipment washwaters.

Directions for Use

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.
Read all Directions for Use carefully before applying.

Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application. For any requirements specific to your state or tribe, consult the agency responsible for pesticide regulation.

Agricultural Use Requirements

Use this product only in accordance with its labeling and with the Worker Protection Standard, 40 CFR part 170. This Standard contains requirements for the protection of agricultural workers on farms, forests, nurseries, and greenhouses, and handlers of agricultural pesticides. It contains requirements for training, decontamination, notification, and emergency assistance. It also contains specific instructions and exceptions pertaining to the statements on this label about personal protective equipment (PPE), and restricted entry interval. The requirements in this box only apply to uses of this product that are covered by the Worker Protection Standard.

Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours. **Exception:** If the product is soil-injected or soil incorporated, the Worker Protection Standard, under certain circumstances, allows workers to enter the treated area if there will be no contact with anything that has been treated.

PPE required for early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil, or water, is:

- Coveralls
- Waterproof gloves
- Shoes plus socks

Storage and Disposal

Do not contaminate water, food, or feed by storage or disposal.
Storage: Store in original container only. In case of leak or spill, contain material with absorbent materials and dispose as waste.
Disposal: Wastes resulting from the use of this product may be disposed of on site according to label use directions or at an approved waste disposal facility.
Container Disposal: When all packets are used, dispose of empty package in a sanitary landfill or by incineration or, if allowed by State and local authorities, by burning. If burned, stay out of smoke.

General Information

Strongarm* herbicide is a selective herbicide for use soil-applied in soybeans and soil-applied or postemergence in peanuts for control of broadleaf weeds.

Use Precautions and Restrictions

Handling Precautions for Water Soluble Packets: Do not remove water soluble packet from overpack except for immediate use. Do not allow water soluble packet to come into contact with water prior to use. Do not handle water soluble packet with wet hands or wet gloves. Carefully reseal overpack containing unopened water soluble packets and protect package from moisture.

- Do not apply more than 0.6 oz per acre of Strongarm as a preplant incorporated, preplant surface or preemergence application in soybeans.
- Do not make more than one soil application during a single growing season in soybeans.
- Do not apply more than 0.45 oz per acre of Strongarm as a preplant incorporated, preplant surface or preemergence application or more than 0.3 oz per acre of Strongarm as a postemergence application in peanuts.
- Do not make more than one soil and one postemergence application during a single growing season in peanuts.

Read and carefully follow all applicable directions, precautions and restrictions on labeling for other products used in combination with Strongarm.

Aerial application of this product is prohibited.

Chemigation: Do not apply this product through any type of irrigation system.

Do not allow livestock to graze treated areas or harvest forage or hay from treated areas.

Iron Chlorosis: There are isolated areas of the country where soil-induced iron chlorosis routinely occurs. Severity of iron chlorosis symptoms may increase when Strongarm is soil-applied in areas with a history of soil-induced iron chlorosis or other nutrient induced crop injury.

Crop Rotation Interval for Common Crops

Crop	Rotation Interval† (Months)
Small grains	4
Corn, Cotton, Rice, Tobacco, Sorghum	18
Sugar beets, Sunflowers	30††

†Minimum number of months that must pass before planting other crops after application of Strongarm at up to 0.6 oz/acre soil-applied, 0.6 oz/acre postemergence, or 0.6 oz/acre soil-applied + 0.3 oz/acre postemergence.

††**Note:** Rotation to sugar beets, sunflowers, and all other crops requires a 30 month rotation interval and a successful field bioassay.

Field Bioassay Instructions: Using typical tillage, seeding practices, and timings for the particular crop, plant several strips of the desired crop variety across the field previously treated with Strongarm. Plant the strips perpendicular to the direction Strongarm was applied. The strips should also be located so that different field conditions are encountered, including differences in soil texture, pH, and drainage. If the crop does not show visible symptoms of injury, stand reduction, or yield reduction, the field can be seeded with the test crop in the growing season following the bioassay. If visible injury, stand reduction, or yield reduction occurs, the test crop should not be seeded, and the bioassay must be repeated the next growing season.

Mixing and Application

Spray Volume and Application

Apply Strongarm in sufficient spray volume to provide uniform coverage. A spray volume of 10 to 40 gallons per acre is recommended for either soil or postemergence applications. Sufficient agitation should be maintained during mixing and spraying to ensure a uniform spray mixture. Apply with ground equipment using standard low pressure (20 to 40 psi) herbicide sprayers equipped with nozzles that provide uniform spray coverage. Screens in spray lines should be no finer than 50 mesh (100 mesh is finer than 50 mesh)..

Strongarm Applied Alone

Strongarm water dispersible granules are provided in water soluble packets that require thorough mixing. **Note:** The water soluble packets are not soluble in liquid fertilizer. If applied in liquid fertilizer, Strongarm **must be** pre-mixed (slurry) with water and then added to the liquid fertilizer solution. Premixing may also be used if making an application in water. See pre-mixing instructions below.

Mixing Instructions:

1. Fill the tank with ½ of the total amount of water or liquid fertilizer for the load.
2. Start the agitation system.
3. Add water soluble packets by opening the overpack and adding water soluble packet (product in transparent film) directly into the spray tank while agitating and allow time to disperse. Do not open water soluble packets. Water soluble packets will float on the surface until the water soluble film dissolves and releases the product. Handling packets with hands should be minimized. Do not handle if hands or gloves are wet. If liquid fertilizer is being used as the spray carrier rather than water, pre-mix the water-soluble packets as described below before adding to tank.
4. After the Strongarm packets have dissolved (approximately 5 minutes) add non-ionic surfactants or other adjuvant materials.
5. Before spraying, make sure packets have completely disintegrated and product is thoroughly mixed with water. Depending on the water temperature and the degree of agitation, the packet and its contents should be completely dispersed within 5 minutes from the time they were added to the water.
6. Continue agitation and completely fill tank.
7. To ensure a uniform spray mixture continuous agitation is required during application. If product is allowed to settle, thoroughly agitate to resuspend the mixture before spraying. Apply within 24 hours of mixing. Weed control with Strongarm which has been mixed and allowed to stand for more than 24 hours may be reduced.

Pre-mixing (Slurry) of Water Soluble Packets: The film used in water soluble packaging for Strongarm is not soluble in liquid fertilizer solutions. In order to add Strongarm to liquid fertilizer carrier, the product **must be** premixed with water. Pre-mixing is also an alternative mixing method for application in water. Use a minimum of 2 quarts of water for up to five 3 oz water soluble packets of Strongarm. The packets can be stirred immediately on addition to water or allowed to dissolve. Stir (or shake if pre-mixed in a closed container) until the packets are completely dissolved and granules are dispersed and then add to the spray tank or inductor (recommended through a 20-35 mesh screen). Rinse container used for pre-mixing and add rinsate to spray tank.

Pre-mixing (other products): If pre-mixing is required for other dry or flowable products applied in tank-mix combination with Strongarm, follow recommendations for pre-mixing of such products provided in their respective product labels.

Strongarm Applied in Tank-mix Combination

Vigorous, continuous agitation during mixing, filling and throughout application is required for all tank-mixes. Sparger type agitators generally provide the most effective agitation in spray tanks. To prevent foaming in the spray tank, avoid stirring or splashing into the spray mixture. To prevent foaming during filling, keep end of fill pipe below the surface of the liquid in the spray tank.

Mixing Order for Tank-mixes:

1. Fill the spray tank to 1/3 of the total spray volume required with water or liquid fertilizer.
2. Start agitation.
3. Add water soluble packets by opening the overpack and adding water soluble packet (product in transparent film) directly into the spray tank while agitating and allow time to disperse. Do not open water soluble packets. Water soluble packets will float on the surface until the water soluble film dissolves and releases the product. Handling packets with hands should be minimized. Do not handle if hands or gloves are wet. If liquid fertilizer is being used as the spray carrier rather than water, pre-mix the water-soluble packets as described above before adding to tank.

4. Add different formulation types in the following order: (1) Other formulation packaged in water soluble film; (2) Any compatibility agent, if required; (3) other dry flowables; (4) wettable powders; (5) aqueous suspensions, flowables and liquids. Maintain agitation and fill spray tank to ¾ of total spray volume and add: (5) emulsifiable concentrates and (6) solutions. Allow time for complete mixing after each addition.
5. Finish filling the spray tank. Maintain continuous agitation during mixing and throughout application.

If application or agitation must be stopped before the spray tank is empty, the materials may settle to the bottom. Settled materials must be re-suspended before spraying is resumed. A sparger agitator is particularly useful for this purpose. Settled material may be more difficult to re-suspend than when originally mixed.

Compatibility Testing:

When tank-mixing Strongarm with other products, a compatibility test (jar test) using relative proportions of the tank-mix ingredients should be conducted prior to mixing the ingredients in the spray tank. Use a compatibility agent if the need for one is indicated by the jar test (ingredients separate readily and are not easily re-dispersed).

Equipment Clean-out Procedures:

1. Drain any remaining spray mixture from the application system.
2. Hose down the interior surfaces of the tank while filling the tank ½ full with water.
3. Add household ammonia at a rate of 1 gallon per 100 gallons of water. Recirculate for 5 minutes and spray out part of this mixture for 5 minutes through the boom. Drain tank.
4. Remove all spray nozzles and screens and clean separately.

Note: If this spray equipment will be used on a crop that is sensitive to Strongarm, steps 1-3 should be repeated. Exterior surfaces of spray equipment should also be washed thoroughly.

All rinsate should be disposed of on site or at an approved waste disposal facility.

SOYBEANS (Soil Application)

Weeds Controlled and Application Rates for Soil Applications of Strongarm in Soybeans:

Weeds Controlled	
bristly starbur	prickly sida
common cocklebur	redroot pigweed
common lambsquarters	smooth pigweed
common ragweed	spurred anoda
elipta	spurge species
Florida beggarweed	velvetleaf
morningglory species	wild poinsetta
nutsedge species[1]	
palmer amaranth	

[1] **Nutsedge control provided only on coarse soils**

Use Rates for Soil Applications, Including Preplant Incorporated, Preplant Surface Applied and Preemergence Applications in Soybeans:

States[1]	Strongarm[2] (pounds/acre)	Strongarm (oz/acre)	Acres per 3.0 oz Packet
AL, AR, DE, FL, GA, KY, LA, MD, MS, NC, NM, OK,SC, TN, TX, VA, MO (Bootheel only)	0.029 - 0.038	0.45 - 0.6	6.7 - 5

[1] Soil applications of Strongarm in other geographies is not recommended.

[2] Soil applications of Strongarm on > 6% organic matter soils may result in reduced weed control and require subsequent postemergence applications of other appropriate herbicides for specific weeds.

[2] Do not use on peat or muck soils.

[2] Severe infestations may require a postemergence application following a soil application for season-long control.

Rate Formula: Acres to be treated ÷ Acres/Packet = Number of Packets

Sample Calculation: Acres = 31
Rate Needed = 0.45 oz/A
Acres/Packet = 6.7 acres/packet
31 acres ÷ 6.7 acres per packet = 4.6 packets (round up to 5 packets)

Note: When the number of packets calculated does not equal a whole number, round to the closest whole number of packets.

Preplant Incorporated Application

Apply Strongarm alone or in tank-mix combination with other herbicides registered for preplant incorporated applications. Apply to a seedbed that is relatively free of clods. Incorporate the herbicide(s) into the top 1 to 3 inches of the final seedbed using equipment that provides thorough soil mixing. Do not apply Strongarm earlier than 4 weeks before planting. For optimum results, apply Strongarm within 2 weeks of planting. When Strongarm is applied in tank-mix combination with other herbicide(s), follow the incorporation directions for the tank-mix partner(s). Follow applicable use instructions, including application rates, precautions and restrictions of each product used in the tank-mixture.

Preplant Surface Application

Apply Strongarm alone or in tank-mix combination with other herbicides registered for preplant soil surface applications. Apply to a seedbed that is relatively free of clods. Do not apply Strongarm earlier than 4 weeks before planting. For optimum results, apply Strongarm within 2 weeks of planting. Soil surface applications are not effective until rainfall of at least 0.25 - 0.5 inches has moved Strongarm into soil where weed germination occurs. If rainfall is not anticipated, shallow (i.e., 2 inches) incorporation prior to planting is recommended to place Strongarm in contact with germinating weeds. If applied in tank-mix combination, follow use instructions, including application rates, precautions and restrictions of each product used in the tank-mixture.

Note: Reduced weed control in the planted row may occur from exposure of untreated soil during the planting operation if surface applications are not incorporated prior to planting.

Burndown Application

When used as a no-till burndown application, Strongarm provides foliar control of specific broadleaf weeds (see weeds controlled list for postemergence application) and residual control of broadleaf weeds listed above for soil applied applications. For optimum results, apply Strongarm within 2 weeks of planting. Foliar burndown can be optimized by using the adjuvant combinations recommended in the directions for postemergence application below. If applied in tank-mix combination with another herbicide(s) for a burndown application, use only adjuvants that are recommended for the tank-mix partner(s). When tank-mixing with other herbicides, a jar test for compatibility is always recommended (see "Compatibility Testing" in the "Mixing Instructions" section).

Preemergence Application

Apply after planting but prior to crop or weed emergence. Strongarm may be applied alone or in tank-mix combination with herbicides registered for preemergence application. When applied in tank-mix combination, follow applicable use instructions, including application rates, precautions and restrictions of each product used in the tank-mixture. For optimum results, Strongarm should be applied within 2 days after planting.

PEANUTS (Soil Application)

Weeds Controlled and Application Rates for Soil Applications of Strongarm in peanuts:

Weeds Controlled	
bristly starbur	prickly sida
common cocklebur	redroot pigweed
common lambsquarters	smooth pigweed
common ragweed	spurred anoda
eclipta	spurge species
Florida beggarweed	velvetleaf
morningglory species	
nutsedge species[1]	
palmer amaranth	

[1] **Nutsedge control provided only in coarse soils.**

Use Rates for Soil Applications, Including Preplant Incorporated and Preemergence Applications in Peanuts:

States[1]	Strongarm[2] (pounds/acre)	Strongarm (oz/acre)	Acres per 3.0 oz Packet
AL, AR, FL, GA, KY, LA, MS, NC, NM, OK, SC, TN, TX, VA, MO (Bootheel only)	0.019 - 0.029	0.3 - 0.45	10.0 - 6.7

[1] Soil applications of Strongarm in other geographies is not recommended.

[2] Soil applications of Strongarm on > 6% organic matter soils may result in reduced weed control and require subsequent postemergence applications of Strongarm or other appropriate herbicides for specific weeds.

[2] Do not use on peat or muck soils.

[2] Severe infestations may require a postemergence application following a soil application for season-long control.

Rate Formula: Acres to be treated ÷ Acres/Packet = Number of Packets

Sample Calculation: Acres = 31
Rate Needed = 0.3 oz/A
Acres/Packet = 10 acres/packet
31 acres ÷ 10 acres per packet = 3.1 packets (round down to 3 packets)

Note: When the number of packets calculated does not equal a whole number, round to the closest whole number of packets.

Preplant Incorporated Application

Apply Strongarm alone or in tank-mix combination with other herbicides registered for preplant incorporated applications. Apply to a seedbed that is relatively free of clods. Incorporate the herbicide(s) into the top 1 to 3 inches of the final seedbed using equipment that provides thorough soil mixing. Do not apply Strongarm earlier than 4 weeks before planting. For optimum results, apply Strongarm within 2 weeks of planting. When Strongarm is applied in tank-mix combination with other herbicide(s), follow the incorporation directions for the tank-mix partner(s). Follow applicable use instructions, including application rates, precautions and restrictions of each product used in the tank-mixture.

Burndown Application

When used as a no-till burndown application, Strongarm provides foliar control of specific broadleaf weeds (see weeds controlled list for postemergence application) and residual control of broadleaf weeds listed above for soil applied applications. For optimum results, apply Strongarm within 2 weeks of planting. Foliar burndown can be optimized by using the adjuvant combinations recommended in the directions for postemergence application below. If applied in tank-mix combination with another herbicide(s) for a burndown application, use only adjuvants that are recommended for the tank-mix partner(s). When tank-mixing with other herbicides, a jar test for compatibility is always recommended (see "Compatibility Testing" in the "Mixing Instructions" section).

Preemergence Application

Apply after planting but prior to crop or weed emergence. Strongarm may be applied alone or in tank-mix combination with herbicides registered for preemergence application. When applied in tank-mix combination, follow applicable use instructions, including application rates, precautions and restrictions of each product used in the tank-mixture. For optimum results, Strongarm should be applied within 2 days after planting.

Peanuts (Postemergence Application)

Adjuvants for Postemergence Use

Either a crop oil concentrate, a non-ionic surfactant must be included in the spray solution.

Crop Oil Concentrate
Apply the crop oil concentrate at 1.25% v/v (10 pt per 100 gal of spray solution). Use a good-quality, petroleum-based or methylated seed oil-based crop oil concentrate with at least 14% emulsifiers and 80% oil.

Non-ionic Surfactant
Use the non-ionic surfactant in the spray solution at a rate (concentration) of 0.25% v/v (2 pt per 100 gal of spray solution). Use only products that contain at least 80% non-ionic surfactant as the active ingredient.

Weeds Controlled for Postemergence Applications of Strongarm in Peanuts:

Weeds Controlled
bristly starbur
common cocklebur
common ragweed
Florida beggarweed
morningglory species
velvetleaf

Use Rates for Postemergence Applications in Peanuts:

States[1]	Strongarm (pounds/acre)	Strongarm (oz/acre)	Acres per 3.0 oz Packet
AL, AR, FL, GA, KY, LA, MS, NC, NM, OK, SC, TN, TX, VT, VA, MO (Bootheel only)	0.009 - 0.019	0.15 - 0.30	20.0 - 10.0

Apply Strongarm as a broadcast spray when weeds are in the 1 to 4 leaf stage and actively growing. Applications made to larger weeds or to weeds under stress may result in unsatisfactory control. Degree of control can be increased by applying Strongarm under good growing conditions (i.e., adequate moisture and temperature). Applications may occur from peanut cracking through pegging.

Strongarm may be applied alone or in tank-mix combination with other postemergence herbicides. Applications of Strongarm must include either a crop oil concentrate, or a non-ionic surfactant.

Rate Formula: Acres to be treated ÷ Acres/Packet = Number of Packets

Sample Calculation: Acres = 31
Rate Needed = 0.3 oz/A
Acres/Packet = 10 acres/packet
31 acres ÷ 10 acres per packet = 3.1 packets (round down to 3 packets)†

Note: When the number of packets calculated does not equal a whole number, round to the closest whole number of packets.

Tank-Mix Options:

For weeds not listed for postemergence control with Strongarm, the other herbicides listed below may be used per label instructions. When applied in tank-mix combination with other herbicides, **follow all use instructions for all products, including application rates, precautions and restrictions for each product used in the tank-mixture, including use of adjuvants.**

Broadleaf Herbicides	Grass Herbicides
Basagran	Select
Blazer	Poast Plus
Pursuit	Assure II*
Starfire	Fusion*
Storm	
Tough	
2,4-DB	

*Under certain conditions, tank-mixing Strongarm with these postemergence grass herbicides may reduce the activity of the grass tank-mix partner. The broadleaf activity of Strongarm will not be affected. Higher rates of the postemergence grass herbicides in a tank-mixture with Strongarm or as sequential applications can be used to overcome the antagonism.

Other Postemergence Herbicide Applications:
Apply other postemergence herbicides at least 7 days before or 7 days after an application of Strongarm.

Warranty Disclaimer

DowElanco warrants that this product conforms to the chemical description on the label and is reasonably fit for the purposes stated on the label when used in strict accordance with the directions, subject to the inherent risks set forth below. DowElanco MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE OR ANY OTHER EXPRESS OR IMPLIED WARRANTY.

Inherent Risks of Use

It is impossible to eliminate all risks associated with use of this product. Crop injury, lack of performance, or other unintended consequences may result because of such factors as use of the product contrary to the label instructions (including adverse conditions noted on the label, such as unfavorable temperatures, soil conditions, etc.), abnormal conditions (such as excessive rainfall, drought, tornadoes, hurricanes), presence of other materials, the manner of application, or other factors, all of which are beyond the control of DowElanco or the seller. All such risks shall be assumed by the buyer.

Limitation of Remedies

The exclusive remedy for losses or damages resulting from the use of this product (including claims based on contract, negligence, strict liability, or other legal theories), shall be limited to, at DowElanco's election, one of the following:

(1) Refund of purchase price paid by buyer or user for product bought, or
(2) Replacement of amount of product used.

DowElanco shall not be liable for losses or damages resulting from handling or use of this product unless DowElanco is promptly notified of such loss or damage in writing. In no case shall DowElanco be liable for consequential or incidental damages or losses.

The terms of the Warranty Disclaimer above and this Limitation of Remedies cannot be varied by any written or verbal statements or agreements. No employee or sales agent of DowElanco or the seller is authorized to vary or exceed the terms of the Warranty Disclaimer or this Limitation of Remedies in any manner.

*Trademark of DowElanco

EPA Accepted __/__/__

Attachment 8

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

December 15, 1999

MEMORANDUM

Subject: **PP6F4784 & PP7F4856**. Request for the use of Diclosulam on Peanut and Soybean. Evaluation of Analytical Methods, Metabolism, and Magnitude of Residue Data.

DP Barcodes	D249626, D249627, D256640	Case No.	288061, 288988
PC Code	129122	Class	Herbicide
Trade Name	STRONGARM*		
MRID #s	441035-01 thru -11, 44103532, 443151-01 thru -03, 44103512, 44103513, 44315104, 44315105		

From: Leung Cheng, Chemist Lee Cheng.
Registration Action Branch 3
Health Effects Division (7509C)

Through: Stephen Dapson, Branch Senior Scientist Stephen C. Dapson 12/15/99
Registration Action Branch 3
Health Effects Division (7509C)

To: Tobi Colvin-Snyder/Jim Tompkins, Team 25
Herbicide Branch
Registration Division (7505C)

Following is the review of a petition from Dow AgroSciences, Inc. requesting establishment of permanent tolerances for residues of the herbicide diclosulam in/on peanut and soybean. The review was performed by the Dynamac Corporation and RAB3, HED. The data assessment has undergone review within RAB3 and has been revised to reflect current HED and OPP policies. If any additional input is needed, please advise.

SUMMARY OF RESIDUE CHEMISTRY DEFICIENCIES

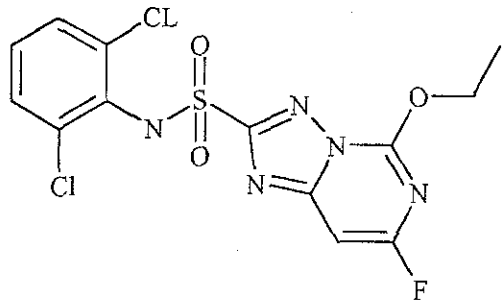
- Revised Section B
- Results of Agency method validation for crops
- Storage time between sampling and analysis for poultry and eggs in the metabolism study; if the storage time was longer than 6 months, evidence should be provided that the identity of residues had not changed during this period between collection and final analysis
- Information on the intervals for which samples and sample extracts were held in frozen storage prior to completion of laboratory analyses. If samples were stored longer than six months from harvest to definitive sample analysis, data demonstrating the storage stability of ^{14}C-residues in rotational crop matrices should accompany the submitted sample storage history
- Analysis of plant metabolism or field trial samples of peanut and soybean for 2,6-dichloroaniline (2,6-DCA) using a validated method at the parts per billion level; data demonstrating the stability of 2,6-DCA in crop matrices if the samples were stored longer than six months

RECOMMENDATIONS

Provided that Section B is revised as specified in Conclusions 2 and 15c, and successful Agency validation of the analytical enforcement method for plants is successful, HED concludes that there are no residue chemistry data requirements that would preclude the establishment of permanent tolerances for residues of diclosulam in peanut and soybean. Registration of Strongarm* should be made conditional upon resolution of the stability of diclosulam residues under frozen storage in the poultry metabolism study and confined rotational crop study, and receipt of confirmatory data for 2,6-DCA in peanut and soybean. A human health risk assessment will be prepared as a separate document.

RD/I:ChemTeam:11/8/99:ChemSAC:12/2/99:SDapson:12/14/99
cc: RAB3 Reading File, PP6F4784, PP7F4856 (peanut), Cheng, Wassell
7509C:RAB3:LCheng:CM#2:RM810A:10/29/99:3rab/diclosulam

DICLOSULAM



PERMANENT TOLERANCE PETITIONS FOR USE ON SOYBEAN (PP#6F4784) AND PEANUT (PP#7F4856)

PC CODE 129122

(DP BARCODE D249626, D249627, D256640)

INTRODUCTION

DowElanco (now Dow AgroSciences) has submitted petitions for the establishment of permanent tolerances for residues of diclosulam (XDE-564) in/on peanut and soybean. Diclosulam is a broad spectrum herbicide for control of broadleaf weeds. The petitioner is also requesting Section 3 registration for an end-use product Strongarm* containing 84% of diclosulam (EPA File Symbol 62719-EII) in a water dispersible granular formulation. Section F of the petitions propose the establishment of tolerances for residues of diclosulam, N-(2,6-dichlorophenyl)-5-ethoxy-7-fluoro[1,2,4]triazolo[1,5-c]pyrimidine-2-sulfonamide, on the following commodities:

Soybean, seed	0.02 ppm
Peanut, nutmeat	.0.02 ppm

Diclosulam is a new triazolopyrimidine sulfonamide herbicide formulated as a water dispersible granule (dry flowable, DF) and proposed for preemergence, preplant incorporated, and postemergence application for the control of broadleaf weeds in peanut and soybean. No tolerances or Codex Maximum Residue Limits (MRLs) are established for residues of diclosulam in/on plant or animal commodities.

CONCLUSIONS

OPPTS 830 Series GLNs: Product Properties

1. The submitted product chemistry data for diclosulam technical grade active ingredient (TGAI), XDE-564, and the formulations are reviewed by Registration Division (D249660, 11/23/98, H. Podall).

OPPTS GLN 860.1200: Proposed Uses

2. The proposed use directions for the 84% DF formulation are inadequate. Use directions for peanuts and soybeans do not specify preharvest intervals (PHIs) following preemergence application to soybeans and postemergence application to peanuts. The label should be amended to include appropriate PHIs following preemergence and postemergence applications to peanuts and soybeans. The available data would support a 30-day PHI (postemergence) for peanuts and a 125-day PHI for soybeans. The label should also be clarified to indicate one preplant or preemergence application in conjunction with one postemergence application to peanuts, as supported by peanut residue data.

OPPTS GLN 860.1300: Nature of the Residue - Plants

3. The nature of diclosulam in plants is adequately understood. Diclosulam was not detected in soybean forage and mature bean. Two metabolites were identified in soybean forage: 7S-[3-aminosulfonyl-5-methoxy[1,2,4]triazolo[1,5-c]pyrimidinyl]cysteine (methyl-ASTP-Cys), a significant metabolite, and 7S-[3-aminosulfonyl-5-ethoxy-[1,2,4]triazolo[1,5-c]pyrimidinyl]cysteine (ASTP-Cys), a minor metabolite. In peanut, the activity levels were much higher in the triazolopyrimidine labeled samples than in the aniline labeled samples. The observation suggested that soil degradates containing the triazolopyrimidine ring system were preferentially taken up by the peanut plants compared to those containing only the aniline portion of the parent molecule. Results showed multiple components at <0.01 ppm and diclosulam was not detected in peanut forage and mature nut.

   The HED Metabolism Assessment Review Committee (MARC) discussed the metabolism of diclosulam in plants and livestock and concluded that diclosulam is the residue of concern in peanut and soybean for enforcement and dietary risk assessment. However, since diclosulam contains a 2,6-dichloroaniline (2,6-DCA) group, the petitioner also needs to provide levels of 2,6-DCA in peanut and soybean at the parts per billion range for dietary risk assessment (MARC memo of 12-6-99, L. Cheng). The petitioner may choose to analyze either plant metabolism or field trial samples of peanut and soybean for 2,6-DCA.

OPPTS GLN 860.1300: Nature of the Residue - Ruminant & Poultry

4. The nature of diclosulam in the ruminant is adequately understood. Only kidney and liver were analyzed for metabolites due to low levels of activity in other tissues. Diclosulam and its 5-hydroxy (or desethyl) metabolite (5-HO-XDE-564) were identified in these two organs. In liver, diclosulam accounted for 19% total radioactive residue or TRR (0.014 ppm) from the aniline label and 17.9% TRR (0.008 ppm) from the triazolopyrimidine label, and its 5-hydroxy metabolite accounted for 18.2% TRR (0.014 ppm) from the aniline label and 13.1% TRR (0.007 ppm) from the triazolopyrimidine label. In kidney, diclosulam was the major residue identified at 48% TRR (0.052 ppm) from the aniline label and 37.6% TRR (0.058 ppm) from the triazolopyrimidine label. Also determined was a minor metabolite, 5-ethoxy-7-fluoro[1,2,4]triazolo[1,5-c]pyrimidine-2-sulfonamide (ASTP, 4.6% TRR, 0.007 ppm) in kidney from the triazolopyrimidine label.

5a. Provided that residues of diclosulam are stable in poultry egg and tissues under frozen storage, the nature of diclosulam in poultry is adequately understood. The petitioner must clarify the storage time between sampling and analysis for poultry and eggs in the metabolism study; if the storage time was longer than 6 months, evidence should be provided that the identity of residues had not changed during this period between collection and final analysis.

5b. ^{14}C-Residue concentrations were higher in skin (0.224-0.225 ppm) and liver (0.179-0.193 ppm), and lower in fat (0.011-0.014 ppm) and muscle (0.026-0.035 ppm). The highest concentrations of ^{14}C-residues in eggs, ~0.023 ppm, were observed on Day-5 for eggs from both aniline and triazolopyrimidine labels.

5c. Overall, >73% of the TRR in tissues and 50-60% in eggs was adequately identified or characterized. The metabolic patterns of the two [^{14}C]diclosulam test substances were qualitatively and quantitatively similar. Parent diclosulam was the principle component of the residue, accounting for 23-27% of the TRR (0.042-0.053 ppm) in liver; 50-66% of the TRR (0.017 ppm) in muscle; 79-88% of the TRR (0.178-0.199 ppm) in skin; 62-94% of the TRR (0.006-0.013 ppm) in fat, and 35-37% of the TRR (0.008 ppm) in eggs. The sulfonamide bridge cleavage product, ASTP, accounted for 8.3-17.6% (0.002-0.023 ppm) in liver, muscle, and eggs from the triazolopyrimidine label. Trace amounts of a putative hydroxyphenyl diclosulam metabolite were also found in all hen matrices at ≤3% of the TRR (≤0.007 ppm).

The HED Metabolism Assessment Review Committee discussed the metabolism of diclosulam in plants and livestock and concluded that finite transfer of diclosulam residues to meat, milk, poultry and eggs is not expected as a result of the proposed use (MARC memo of 12-6-99, L. Cheng). Tolerances in livestock and feeding studies are not required as a result of the proposed use. The Committee also concluded that should feeding studies be necessary in the future, diclosulam should

be determined. Furthermore, for dietary exposure assessment in ruminant liver, the level of diclosulam will be doubled to account for 5-hydroxy diclosulam.

OPPTS GLN 860.1340: Analytical Methods

6. The method validation conducted using peanut matrices is sufficient to demonstrate the potential of GRM 96.01 and 94.19 as enforcement methods. The registrant is required to submit a sample each of diclosulam, N-methyl diclosulam, and N-ethyl diclosulam. A radiovalidation study in plant matrices is not required for this petition since none of the plant metabolism samples contained quantifiable diclosulam. A radiovalidation study in livestock matrices is also not required since livestock tolerances are not required for this petition. However, for future uses on crops in which finite levels of diclosulam occur in plants and livestock, radiovalidation studies will be needed as stated under 860.1340. A PMV of methods GRM 96.01 and 94.19 has been requested for diclosulam.

OPPTS GLN 860.1360: Multiresidue Method

7. The registrant has submitted data pertaining to the multiresidue methods testing of diclosulam. The registrant stated that diclosulam was recovered through Protocol C but could not be recovered from Protocol D, E, F due to its lack of mobility on Florisil column and/or lack of sensitivity to the detector. HED has forwarded these data to FDA for review.

OPPTS GLN 860.1380: Storage Stability Data

8. The submitted storage stability data for plants are adequate and indicate that residues of diclosulam *per se* are stable when stored at ~-20 C in soybean seed, forage, and hay for up to 1 year. The maximum storage intervals and conditions of the residue studies are adequately supported by the available data. Samples of peanut commodities were stored frozen (~-20 C) for up to 39 days, and samples of soybean commodities were stored frozen under similar conditions for up to 245 days (8 months).

OPPTS GLN 860.1480: Meat/Milk/Poultry/Eggs

9. Based on results from the animal metabolism studies and the maximum theoretical dietary exposure (0.02 ppm or less, *ca.* 500-700x exaggeration) for livestock resulting from the proposed uses on peanut and soybean, there is no reasonable expectation of finite diclosulam residues being transferred to animal commodities. Therefore, tolerances for residues in livestock are not required at this time.

OPPTS GLN 860.1500: Crop Field Trials

10. Soybean. The submitted soybean field trial data are adequate. Residues of diclosulam were <0.003 ppm (<LOD) in/on all soybean seed samples (n=81) harvested 125-158 days after a single preplant incorporated or preemergence application of diclosulam (83.4 or 84.2% DF) at 0.031-0.047 lb ai/A (1-1.5x the proposed maximum seasonal rate). Residues were <0.003 ppm (<LOD) in/on all soybean forage and hay samples (n=3 each) harvested 83-102 days after a single preplant incorporated treatment at 0.038-0.047 lb ai/A (1-1.5x). The proposed tolerance at 0.02 ppm in/on soybean is adequate.

11. Peanut. The submitted peanut field trial data are adequate. Residues of diclosulam were <0.003 ppm (<LOD) and <0.006-0.765 ppm in/on 22 samples each of peanut nutmeat and hay harvested 16-32 days after a split application of diclosulam (84.2% DF) consisting of a preplant incorporated or preemergence treatment at 0.031 lb ai/A followed 81-144 days later by a postemergence treatment at 0.024 lb ai/A, for a total of 0.055 lb ai/A (1.4x the proposed rate). The proposed tolerance at 0.02 ppm in/on peanut nutmeat is adequate.

12. The proposed label includes a restriction against grazing treated areas or harvesting forage and hay from treated areas; therefore, no tolerances for diclosulam residues in/on peanut hay and in/on soybean forage or hay are required at this time.

OPPTS GLN 860:1520: Processed Food/Feed

13. Soybean. The submitted soybean processing studies are adequate and indicate that residues of diclosulam do not concentrate in soybean processed commodities. Residues of diclosulam were <0.003 ppm (<LOD) in/on two soybean seed samples harvested 99-127 days after a single at planting preemergence application of diclosulam (83.4 and 84.0% DF) at 0.09 or 0.25 lb ai/A (~3x or ~8x the proposed rate). Residues were <0.003 ppm (<LOD) in each of two meal, hull, refined oil samples processed from the treated soybean RAC samples. No tolerances for residues of diclosulam in soybean processed commodities are required.

14. Peanut. The submitted peanut processing study is adequate. Residues of diclosulam were <0.003 ppm (<LOD) in/on four nutmeat samples harvested 30 days after split pre- and postemergence applications of diclosulam (84.2% DF) totaling 0.17 lb ai/A (4.3x the proposed rate). Peanut processed fractions were not generated. As all peanut nutmeat samples from the RAC field trials and exaggerated rate trials had residues of diclosulam at <0.003 ppm (<LOD), no tolerances for residues of diclosulam in peanut processed commodities are required.

OPPTS GLN 860.1850 and 860.1900: Confined/Field Accumulation in Rotational Crops

15a. The confined rotational crop study is adequate provided the petitioner furnishes information on the intervals for which samples and sample extracts were held in frozen storage prior to completion of laboratory analyses. If samples were stored longer than six months from harvest to definitive sample analysis, data demonstrating the storage stability of ^{14}C-residues in rotational crop matrices should accompany the submitted sample storage history.

15b. Following a soil application of [aniline-^{14}C] or [triazolopyrimidine-7,9-^{14}C]diclosulam at 0.050 lb ai/A (1.25x the maximum seasonal rate), radioactive residues were low (<0.05 ppm) in wheat and potato RAC samples from the 120-day plantback interval (PBI), with the exception of [triazolopyrimidine-7,9-^{14}C]-treated wheat straw (0.070 ppm). ^{14}C-Residues in wheat and potato RACs resulting from the application of [aniline-^{14}C]diclosulam were lower (<0.003-0.007 ppm) than ^{14}C-residues resulting from the application of [triazolopyrimidine-7,9-^{14}C]diclosulam (0.008-0.070 ppm). For crops harvested from the [triazolopyrimidine-7,9-^{14}C]treated 120-day PBI plots, ^{14}C-residues were 0.008 ppm in potato tubers and 0.020, 0.025, and 0.070 ppm in wheat forage, grain, and straw, respectively. Lettuce crops planted at 120-, 161-, and 225-day PBIs failed due to phytotoxicity; Swiss chard planted at a 225-day PBI had ^{14}C-residues of 0.012-0.024 ppm but was stunted due to phytotoxicity.

Wheat and potato RAC samples containing radioactivity approaching or exceeding 0.01 ppm were adequately characterized by solvent extraction and HPLC analyses. No parent compound was detected. Minor unknown peaks (each at ≤0.009 ppm) were detected in aqueous and organic fractions of wheat forage and straw, along with a polar peak (R_t=3.0 min) from the wheat grain aqueous fraction containing 0.01 ppm. Further characterization efforts were made on post-extraction solids of wheat grain and straw (each ≤43.3%TRR, <0.02 ppm) indicating that ^{14}C-residues were incorporated as natural components (starch, lignin, and cellulose). Although characterization of ^{14}C-residues in a representative leafy vegetable was not achieved and no attempt was made to obtain samples of a leafy vegetable at PBIs longer than 225 days, no additional data on ^{14}C-residues in a rotated leafy vegetable are required for purposes of this petition. Tolerances for rotational crops are not required as long as the label specifies PBIs of 120 days.

15c. Due to the phytotoxicity of diclosulam to susceptible crops, the petitioner is proposing relatively long plantback restrictions for rotated crops: 4 months for small grains, 9 months for cotton, soybeans, and peanuts; 18 months for corn, rice, tobacco, and sorghum; and 30 months for all other crops. RAB3 has no objections to these plantback restrictions. However, the petitioner needs to define "small grains" as wheat, barley, oat and rye.

16. As there are no Canadian, Mexican and Codex MRLs established for residues of diclosulam in/on peanuts and soybeans, no compatibility problem with U.S. tolerances exists at this time.

DETAILED CONSIDERATIONS

OPPTS 830 Series GLNs: Product Properties

The submitted product chemistry data for diclosulam technical grade active ingredient (TGAI) and the formulations are reviewed by Registration Division (D249660, 11/23/98, H. Podall).

OPPTS GLN 860.1200: Proposed Uses

The petitioner provided a specimen label for a 84% water dispersible granule (dry flowable; DF) formulation (STRONGARM™; EPA Reg. No. 62719-XXX; dated 11/17/98) including proposed uses on peanuts and soybeans for broadleaf weed control.

For peanuts, the 84% DF allows a maximum of one preplant incorporated, preplant surface, or preemergence application at 0.016-0.024 lb ai/A; the herbicide should be incorporated into the top 1 to 3 inches of the seedbed within 2 weeks of planting (preplant), or applied within 2 days after planting (preemergent). The herbicide may also be applied at the peanut cracking through pegging stage when weeds are in the 1 to 4 leaf stage and actively growing as a broadcast spray at 0.008-0.016 lb ai/A; however, the maximum number of postemergent applications is not specified.

For soybeans, the 84% DF allows a maximum of one preplant incorporated, preplant surface, or preemergence application at 0.024-0.032 lb ai/A/season.

Preharvest intervals (PHIs) are not specified for either soybeans or peanuts.

The label indicates that applications may be made with ground equipment using a sufficient spray volume (≥10 gal of water/A recommended) to provide uniform coverage. For postemergence applications, either a crop oil concentrate at 1.25% v/v or a non-ionic surfactant at 0.25% v/v must be included in the spray mixture. The label prohibits application of diclosulam by aerial means or through any type of irrigation system, and to muck or peat soils. The label also prohibits the grazing of livestock and the harvest of forage and hay in treated areas.

The label specifies minimum plantback intervals (PBIs) for various crops following a preplant or preemergence soil application at up to 0.032 lb ai/A for soybeans and 0.024 lb ai/A for peanuts. No mention is made under the rotational crop restrictions of the 0.016 lb ai/A postemergence application allowed on peanuts. The following minimum PBIs are specified: 4 months for small

grains; 9 months for cotton, peanuts, and soybeans; and 18 months for corn, rice, tobacco, and sorghum. For sugar beets, sunflowers, and all other crops, a minimum PBI of 30 months is specified in conjunction with a successful field bioassay to evaluate for phytotoxicity.

A restricted entry interval of 12 hours is specified on the proposed label.

Conclusions: The proposed use directions for the 84% DF formulation are inadequate. Use directions for peanuts and soybeans do not specify preharvest intervals (PHIs) following preemergence application to soybeans and postemergence application to peanuts. The label should be amended to include appropriate PHIs following preemergence and postemergence applications to peanuts and soybeans. The available data would support a 30-day PHI for peanuts (postemergence) and a 125-day PHI for soybeans. The label should also be clarified to indicate one preplant or preemergence application in conjunction with one postemergence application to peanuts, as supported by peanut residue data. (See **Confined Accumulation in Rotational Crops** for comment on the definition of small grains.)

OPPTS GLN 860.1300: Nature of the Residue - Plants

Soybean

> 44103504 Stafford, L. et al. (1996) [^{14}C]XDE-564 Nature of Residue Study in Soybeans: Laboratory Study ID MET93038/MET94016. Unpublished study prepared by DowElanco 126 pp

The in-life phase and the analytical phase of the field study were conducted by the registrant at the Greenfield, IN site. Additional experiments were conducted with soybean plants in a greenhouse and with soybean cell cultures to further characterize the residual components of the forage.

Field study

Test plots were located at the registrant's Greenfield, Indiana Field Station. Dimensions of the plots were 1.5 x 3.0 m. XDE-564 was mixed with radiolabeled test material "A" (carbon-14 in the phenyl or aniline ring, sp act: 24.2 mCi/mmol; 99.1-99.4% radiochemical purity) or "TP" (carbon-14 in the triazolopyrimidine ring, sp act: 23.3 mCi/mmol; 99.5-99.6% radiochemical purity), yielding 8.06 mCi/mmol for "A" and 8.09 mCi/mmol for "TP". On the day of application, the test substances were dissolved in acetonitrile and then diluted with water. An aliquot was removed for liquid scintillation counting (LSC) and thin layer chromatography (TLC) analysis for concentration, stability and purity. The test solutions were applied to the soil, equivalent to a rate of 158 g ai/ha (0.14 lb ai/A, 4.4x exaggeration). XDE-564 was incorporated into each plot to a depth of about 4-6 cm by raking the soil surface in two directions. Soybean seeds were then planted in 2 rows per plot approximately 5 cm deep and 2-5 cm apart with 76 cm (30-inch) row spacing. A control plot was seeded in the same manner in soil which had not been treated with XDE-564.

Plant specimens were collected on June 23, July 22, August 3, and October 12, 1993. Samples of early forage (late V2 developmental stage) were collected on day 33 and samples of bloom-stage forage (V9 stage) were collected on day 62. The forage samples were put in plastic bags and shipped over ice to the laboratory (Global Environmental Chemistry Laboratory, DowElanco, Indianapolis, IN). The soybeans were harvested on day 145. Bean pods and stems (cut into small pieces) were collected and shipped (apparently not chilled) to the laboratory.

The forage samples were washed with water, blotted dry and weighed. The specimens were then immersed in liquid nitrogen and ground in a mortar with a pestle. After evaporation of the nitrogen, aliquots of the forage were analyzed for total radioactivity (TRR). In one scheme, the forage was extracted in 3:1 acetonitrile:water under reflux. The mixture was filtered, and the filtrate was partitioned twice against methylene chloride. The aqueous phase was adjusted to pH 2 with hydrochloric acid and partitioned against ethyl acetate. The aqueous phase was extracted with ethyl acetate after adjusting to pH 7 and pH 10. In a second scheme, the forage was homogenized in the presence of 8:2 acetonitrile:water. The homogenate was centrifuged and the supernatant decanted. The process was repeated two additional times. The supernatants were combined and concentrated to remove the acetonitrile. The aqueous phase was adjusted to pH <2 with hydrochloric acid before partitioning against ethyl acetate three times. The organic extracts were combined.

The mature beans were manually separated from the hulls. The beans were chilled in a -20 C freezer before grinding with liquid nitrogen in a Fitzmill. After evaporation of the nitrogen, aliquots were analyzed for TRR by combustion/LSC. The ground mature beans were stirred in methylene chloride, vacuum filtered, and the filtrate was concentrated before LSC. The post-extraction solids (PES) were extracted with 75:25:1 acetonitrile:water:hydrochloric acid under reflux. The mixture was filtered, and the filtrate was concentrated to remove acetonitrile, adjusted to pH 2 with hydrochloric acid and partitioned against ethyl acetate. The aqueous phase was adjusted to pH 7 with 1N sodium hydroxide and partitioned against ethyl acetate twice.

Table 1. Distribution and characterization/identification of ^{14}C-residues in soybean forage and seed treated with phenyl labeled XDE-564 ("A") or triazolopyrimidine labeled XDE-564 ("TP") at 158 g ai/ha (0.14 lb ai/A)

Fraction	%TRR	ppm	Characterization/Identification
"A" 33 DAT Forage (0.060 ppm)			
ACN/water	69.0	0.041	
CH_2Cl_2	17.4	0.010	
EtOAc/pH2	19.4	0.012	
EtOAc/pH7			
EtOAc/pH10			
Aqueous	31.9	0.019	
Insoluble	25.7	0.015	

Fraction	%TRR	ppm	Characterization/Identification
"TP" 33 DAT Forage (0.071 ppm)			
ACN/water	73.5	0.052	
CH_2Cl_2	8.2	0.006	
EtOAc/pH2	4.2	0.003	
EtOAc/pH7			
EtOAc/pH10			
Aqueous	42.7	0.030	metabolite D (major), C (minor), other minor components
Insoluble	22.4	0.016	
"A" 62 DAT Forage (0.015 ppm)			
ACN/water	55.8	0.008	
CH_2Cl_2	13.8	0.002	
EtOAc/pH2	20.9	0.003	
EtOAc/pH7			
EtOAc/pH10			
Aqueous	21.1	0.003	
Insoluble	39.2	0.006	
"TP" 62 DAT Forage (0.029 ppm)			
ACN/water	38.1	0.011	
CH_2Cl_2	7.8	0.002	
EtOAc/pH2	11.1	0.003	
EtOAc/pH7			
EtOAc/pH10			
Aqueous	44.8	0.013	
Insoluble	43.2	0.013	
"A" 145 DAT Mature Bean (0.009 ppm)			
CH_2Cl_2	13.5	0.001	
ACN/water/acid			
EtOAc/pH2	7.0	0.001	
EtOAc/pH7			
Aqueous	4.5	<0.001	
Insoluble	70.6	0.006	
"TP" 145 DAT Mature Bean (0.015 ppm)			
CH_2Cl_2	6.7	0.001	
ACN/water/acid			
EtOAc/pH2	9.7	0.001	
EtOAc/pH7			
Aqueous	15.2	0.002	

Fraction	%TRR	ppm	Characterization/Identification
Insoluble	60.6	0.009	

A substantial portion of the activity in forage samples partitioned into the aqueous phase. The aqueous fraction of the day 33 forage sample (*ca.* 40% TRR) from the "TP" study using the second extraction scheme was analyzed by reversed phase HPLC. The chromatogram showed a major component (metabolite D, methyl-ASTP-Cys, *ca* 21%) along with a mixture of minor components (containing metabolite C, ASTP-Cys, *ca* 5%). For mature bean, the report stated that all the fractions in soybean seed contained <0.01 ppm; therefore, not enough activity was present to warrant identification of the metabolites.

Greenhouse Experiment

The greenhouse experiment was conducted because the field study did not supply enough early forage samples (V2 growth stage, day 33) for metabolite identification. The specific activity of "A" (XDE-564 labeled in the phenyl ring) was 41,800 dpm/μg and for "TP" was 41,000 dpm/μg, and the respective radiochemical purity was 95.8-96.9% and 96.3096.9%. Each test substance was applied to soil and a portion of the treated soil was added to each of fifty 13-cm diameter pots containing untreated soil and 7 soybean seeds. The amount of XDE-564 applied is equivalent to 350 g ai/ha or 8x the maximum proposed preemergence rate of 44 g ai/ha.

Specimens were taken at day 14, 21, and 28 from the test plots. The 28-day samples represent an early stage (V2) of soybean plant. Fractionation was similar to the alternate scheme that was used for extracting field grown soybean forage (started with 8:2 acetonitrile: water).

Table 2. Distribution and characterization/identification of ^{14}C-residues in greenhouse soybean forage treated with phenyl labeled XDE-564 ("A") or triazolopyrimidine labeled XDE-564 ("TP") at 350 g ai/ha (8x).

Fraction	%TRR	ppm	Characterization/Identification
"A" 14 DAT Forage (0.563 ppm)			
ACN/water	90.1	0.507	
Hexane	0.3	0.002	
EtOAc/pH2	44.4	0.250	
Aqueous	32.0	0.180	HPLC: metabolite C & D not present
Insoluble	27.8	0.157	
"TP" 14 DAT Forage (0.567 ppm)			
ACN/water	81.6	0.463	
Hexane	0.3	0.002	
EtOAc/pH2	26.8	0.152	

Fraction	%TRR	ppm	Characterization/Identification
Aqueous	42.7	0.242	HPLC: metabolite C & D
Insoluble	21.5	0.121	
"A" 21 DAT Forage (0.441 ppm)			
ACN/water	91.9	0.409	
EtOAc/pH2	56.0	0.249	
Aqueous	30.0	0.133	HPLC: metabolite C & D not present
Insoluble	14.3	0.064	
"TP" 21 DAT Forage (0.410 ppm)			
ACN/water	85.1	0.352	
EtOAc/pH2	33.5	0.139	
Aqueous	51.1	0.212	HPLC: metabolite C & D
Insoluble	20.0	0.089	
"A" 28 DAT Forage (0.264 ppm)			
ACN/water	80.9	0.216	
EtOAc/pH2	48.2	0.129	
Aqueous	17.9	0.048	HPLC: metabolite C & D not present
Insoluble	14.1	0.038	
"TP" 28 DAT (0.225 ppm)			
ACN/water	80.7	0.183	
EtOAc/pH2	24.4	0.055	
Aqueous	54.8	0.124	HPLC: metabolite C & D
Insoluble	18.0	0.048	

The aqueous phases were analyzed by HPLC which showed the presence of metabolites C and D in the "TP" samples but not in the "A" samples. D was the major component and matched the retention time of the major component observed in the day 33 field forage sample. Therefore, metabolite D was purified and isolated (C_{18} SepPak column, Sephadex, HPLC and preparative TLC) for structural identification. LC/MS analysis showed a radioactive peak exhibiting ions at *m/z* 371 and 349. Examination of the positive ion mass spectrum led to the assignment of *m/z* 371 as the sodium adduct and *m/z* 349 as the M+H ion. The report concluded the likely structure of D as 7S-[3-aminosulfonyl-5-methoxy[1,2,4]triazolo[1,5-c]-pyrimidinyl]cysteine (methyl-ASTP-Cys). From the date on the HPLC histogram, RAB3 estimated that the isolation and identification of metabolite D was completed roughly 4 months after forage sample collection. (For identification of metabolite C, see the following paragraph.)

Cell Culture Experiment

The cell culture experiment was conducted to verify that the "TP"-labeled metabolites found in soybean plants originated from the soil. Studies of the soil metabolism and terrestrial dissipation of XDE-564 showed 5-ethoxy-7-fluoro[1,2,4]triazolo[1,5-c]pyrimidine-2-sulfonamide (ASTP) to be a significant metabolite, demonstrating the bond cleavage between the aniline and triazolopyrimidine rings. The ASTP isolated from the soil metabolism study was used in the cell culture study (7-day incubation sample) to generate metabolite C for identification. Subsequent to extraction and purification, LC/MS analysis of the unknown showed a *m/z 363*, which corresponded to M+1 of ASTP-cys (conjugation with homoglutathione). From the date on the HPLC histogram, RAB3 estimated that the isolation and identification of metabolite C was completed within 4 months after sample collection.

The materials used to treat the soybean cell cultures were "A", "TP", extracts from day 28 "A" greenhouse soil, extracts from day 28 "TP" greenhouse soil, and ASTP isolated from day 28 "TP" greenhouse soil. Soybean cell cultures were incubated for 3, 7, and 14 days in the presence of "A", "TP", "A"-soil extract and "TP"-soil extract. After incubation at 25 C, the cell cultures were separated into cells and media. The cells were extracted with 8:2 acetonitrile:water and the resultant fractions were analyzed for radioactivity. The majority of the radioactivity was present in the cell soluble fraction suggesting that the test materials penetrated the cell walls and were available for metabolism.

All the soluble fractions were analyzed by HPLC. Results showed formation of specific metabolites in the soil extracts from the "A" and "TP" which were not present in the "A" and "TP" experiments. The report concluded that the soil metabolites taken up into soybean were eventually metabolized.

Peanut

44315102 Stafford, L. and Lardie, T. (1997) XDE-564: A Nature of the Residue Study in Peanuts Following Preplant Incorporation and Postemergence Treatment with ^{14}C-Labeled XDE-564: Laboratory Study ID RES95078. Unpublished study prepared by DowElanco 59 pp

The test plots were located at the Dow Agrosciences, Wayside, Mississippi Field Station. For pre-plant incorporations (PPI; 5/10/95), diclosulam ("A"=86800 dpm/μg, 98.8-99.2% radiochemical purity; "TP"=85500 dpm/μg, 98-98.8% radiochemical purity) was applied to the soil via an XR 8002 VS TeeJet nozzle pressured by nitrogen at a rate equivalent to 78 g ai/ha (0.07 lb ai/A, 3x the proposed PPI rate). XDE-564 was mixed into the soil to a depth of about 1 inch by raking the surface. Peanut seeds were then planted in rows approximately 1 inch deep and 1 inch apart. On 6/23/95, immediately after the immature forage samples had been taken, DXE-564 was applied as a postemergence application, also through the nitrogen-propelled nozzle, to the previously treated (PPI) test plots at a rate equivalent to 52 g ai/ha (0.047 lb ai/A, 3x the proposed post-emergence rate). Samples of early forage (43 days after planting), forage (91 days), and mature peanut (153 days) were collected. A control plot was seeded in the same manner in soil which had not been treated with XDE-564.

Table 3. Distribution and characterization/identification of ^{14}C-residues in peanut forage and seed treated with phenyl labeled XDE-564 ("A") or triazolopyrimidine labeled XDE-564 ("TP") at 78 g ai/ha PPI and 52 g ai/ha postemergence.

Fraction	%TRR	ppm	Characterization/Identification
"TP" 43 DAP Forage (0.111 ppm)			
ACN/water	61.2	0.068	
water/pH2	39.1	0.043	
EtOAc/pH2	28.2	0.031	
Insoluble	17.7	0.020	
"A" 91 DAP Forage (0.042 ppm)			
ACN/water			
water/pH2	19.0	0.008	
EtOAc/pH2	25.8	0.011	
Insoluble	46.5	0.020	
"TP" 91 DAP Forage (0.103 ppm)			
ACN/water			
water/pH2	34.9	0.036	
EtOAc/pH2	15.3	0.016	
Insoluble	50.8	0.052	
"A" 153 DAP Mature Nutmeat (0.015 ppm)			
Hexane	41.4	0.006	
ACN/hexane			
Hexane			
ACN	38.9	0.006	
ACN/water	5.1	<0.001	
Insoluble	51.7	0.008	
"TP" 153 DAP Mature Nutmeat (0.026 ppm)			
Hexane	28.0	0.007	
ACN/hexane			
Hexane			
ACN	22.2	0.006	
ACN/water	21.9	0.006	
Insoluble	49.2	0.013	

Conclusion: The nature of the residue in plants is adequately understood. Diclosulam was not detected in soybean forage and mature bean. Two metabolites were identified in soybean

forage: 7S-[3-aminosulfonyl-5-methoxy[1,2,4]triazolo[1,5-c]-pyrimidinyl]-cysteine (methyl-ASTP-Cys), a significant metabolite, and 7S-[3-aminosulfonyl-5-ethoxy-[1,2,4]triazolo[1,5-c]pyrimidinyl]-cysteine (ASTP-Cys), a minor metabolite. In peanut, the activity levels were much higher in the triazolopyrimidine labeled samples than in the aniline labeled samples. The observation suggested that soil degradates containing the triazolopyrimidine ring system were preferentially taken up by the peanut plants compared to those containing only the aniline portion of the parent molecule. Results showed multiple components at < 0.01 ppm and diclosulam was not detected in peanut forage and mature nut.

The HED Metabolism Assessment Review Committee (MARC) discussed the metabolism of diclosulam in plants and livestock and concluded that diclosulam is the residue of concern in peanut and soybean for enforcement and dietary risk assessment. However, since diclosulam contains a 2,6-dichloroaniline (2,6-DCA) group, the petitioner also needs to provide levels of 2,6-DCA in peanut and soybean at the parts per billion range for dietary risk assessment (MARC memo of 12-6-99, L. Cheng). The petitioner may choose to re-analyze either the plant metabolism or field trial samples of peanut and soybean for 2,6-DCA.

860.1300: Nature of the Residue in Animals

Lactating goats

> 44103506 Finney-Brink, K. (1996) Nature of the Residue of [^{14}C]XDE-564 in Lactating Goats: Laboratory Study ID MET94019. Unpublished study prepared by DowElanco and ABC Laboratories. 203 pp

The in-life phase of the metabolism study was conducted by ABC Laboratories, Inc, Columbia, MO, and the metabolism study samples (except for the homogenization and the determination of the total radioactive residue) were analyzed in the Residue Chemistry Laboratories of DowElanco. The radioactive test substances (aniline-^{14}C-XDE-564, 24.2 mCi/mmol, and triazolopyrimidine-^{14}C-XDE-564, 23.3 mCi/mmol, both uniformly labeled in the aromatic rings with >98.6% chemical purity) were reduced to 8.49 mCi/mmol and 8.82 mCi/mmol with XDE-564 before given to the test animals.

The study consisted of two treated and one untreated lactating goats. The animals were acclimated to the test stalls for at least 7 days before dosing. Goat II-A was fed aniline-^{14}C-XDE-564 and goat III-TP was fed triazolopyrimidine-^{14}C-XDE-564 in the form of capsules for 5 consecutive days at a nominal concentration of 10 ppm based on the feed (alfalfa cube and grain) intake. Goat I-C was fed a daily dose of a placebo capsule. The maximum dietary burden for dairy cattle was calculated to be 0.014 ppm XDE-564 assuming a residue level of 0.02 ppm in peanut meal, soybean seed, soybean meal and hulls, and following the percent diet (15%, 15%, 15% and 20%) and dry matter content (85%, 89%, 92% and 90%) given in Table 1 of the 860.1000 Guidelines. Dosing started on the morning of 3/18/94 and the test animals were sacrificed on the morning of 3/23/94.

Each animal was hand milked twice a day and the a.m. and p.m. milk from each day were kept separate. The animals were electrocuted within 24 hours of the last dose. Samples of muscle (longissimus dorsi, semimembranosus, triceps), fat (omental, perirenal), kidney, and liver were collected. After sample preparation, aliquots were removed for radioanalysis while the remaining samples were shipped to DowElanco, stored frozen before and after radioanalysis.

The concentrations of XDE-564 in the milk and tissues are summarized in Table 4. Even when the animals were fed such an exaggerated dose of XDE-564 (~700x), tissue residues were very low. Residues in the milk were also extremely low (<0.001-0.005 ppm), and never exceeded 0.005 ppm in either "A" or "TP" treated samples. Data indicate that diclosulam does not appear to accumulate in milk.

Table 4. Total radioactive residues in milk and tissues of goats dosed for 5 days with [UL-aniline-^{14}C] or [triazolopyrimidine-7,9-^{14}C] XDE-564 at 10 ppm

Matrix	Total Radioactive Residues (ppm)	
	"A"	"TP"
Milk	0.003	0.002
Muscle	0.008	0.009
Fat	0.005	0.011
Kidney	0.109	0.154
Liver	0.074	0.046

Analysis of metabolites was conducted through reverse phase HPLC connected to a UV detector or radioactivity monitor, and TLC by UV detection. After initial solvent extractions of kidney and liver, the tissue samples were further treated with pronase E (Sigma Chemical).

In order to identify some of the metabolites found in the ruminant tissues, especially liver, a composite urine sample was prepared by combining three urine samples (day 2, day 3, and day 5 from the "TP" experiment) for metabolite isolation and identification. The urine sample was extracted with ethyl acetate and the metabolites were separated into fractions by silica gel chromatography. Fractions containing radioactive components of similar polarity were pooled. A specific pooled fraction was further purified by HPLC to yield a urine metabolite for mass spectral identification. The metabolite was identified as 5-hydroxy (or 5-desethyl) of the parent compound (5-OH-XDE-564) by its retention time on HPLC with a non-radiolabeled reference standard, and a prominent mass spectral peak corresponding to *m/z* 378 (mol wt of 5-OH-XDE-564 + 1), along with an additional fragmentation peak at *m/z* 161 (dichloroaniline group).

The liver and kidney samples were extracted within 10 days of receipt and the organic and aqueous phases were analyzed by HPLC within 21 days afterwards. Further fractionation and

characterization of the sample was conducted within the next 6 months. The distribution and characterization/identification of metabolites are summarized in Table 5 and 6.

Table 5. Distribution and characterization/identification of ^{14}C-residues in liver with phenyl labeled XDE-564 ("A") or triazolopyrimidine labeled XDE-564 ("TP") at 10 ppm.

Fraction	%TRR	ppm	Characterization/Identification
"A" (0.074 ppm)			
ACN/water	49.3	0.037	
Hexane	0	0	
EtOAc (Org-1)	29.7	0.022	18.4% (0.014 ppm) XDE-564, 9.3% (0.007 ppm) 5-OH-XDE-564, 0.7% (<0.001 ppm) unknown, 1.3% (0.001 ppm) multiple unknowns
Aqueous-1	5.5	0.004	3.6% (0.003 ppm) 5-OH-XDE-564, 1.9% (0.001 ppm) multiple unknowns
Insoluble			subjected to aqueous acetone extraction, buffer rinse, enzyme and acid treatments
EtOAc (Org-2)	11.5	0.009	0.6 (<0.001 ppm) XDE-564, 5.3% (0.004 ppm) 5-OH-XDE-564, 1.4% (0.001 ppm) and 2.8% (0.002 ppm) single unknowns, 1.4% (0.001 ppm) multiple unknowns
Aqueous-2	2.4	0.002	1.3% (0.001 ppm) unknown, 1.1% (0.001 ppm) multiple unknowns
EtOAc (Org-3)	4.8	0.004	multiple unknowns
Aqueous-3	14.4	0.011	multiple unknowns
Residue	21.2	0.016	multiple unknowns
"TP"(0.046 ppm)			
ACN/water	50.4	0.023	
Hexane	0	0	
EtOAc (Org-1)	28.6	0.013	16.3% (0.007 ppm) XDE-564, 8.0% (0.004 ppm) 5-OH-XDE-564, 1.1% (0.001 ppm) unknown, 3.2% (0.001 ppm) multiple unknowns
Aqueous-1	4.0	0.002	1.5% (0.001 ppm) 5-OH-XDE-564, 2.5% (0.001 ppm) multiple unknowns
Insoluble			subjected to aqueous acetone extraction, buffer rinse, enzyme and acid treatments
EtOAc (Org-2)	12.9	0.006	1.6 (0.001 ppm) XDE-564, 3.6% (0.002 ppm) 5-OH-XDE-564, 0.5% (<0.001 ppm) and 4.9% (0.002 ppm) single unknowns, 2.3% (0.001 ppm) multiple unknowns
Aqueous-2	2.2	0.001	2.2% (0.001 ppm) multiple unknowns
EtOAc (Org-3)	4.1	0.002	multiple unknowns
Aqueous-3	20.7	0.010	multiple unknowns
Residue	21.4	0.010	multiple unknowns

Table 6. Distribution and characterization/identification of ^{14}C-residues in kidney with phenyl labeled XDE-564 ("A") or triazolopyrimidine labeled XDE-564 ("TP") at 10 ppm.

Fraction	%TRR	ppm	Characterization/Identification
"A" (0.109 ppm)			
ACN/water	65.9	0.065	
Hexane	2.2	0.002	
EtOAc (Org-1)	51	0.056	48% (0.052 ppm) XDE-564, 6 single unknowns at 0.1-1.0%
Aqueous-1	1.2	0.001	single unknown
Insoluble			subjected to aqueous acetone extraction, buffer rinse, enzyme and acid treatments
EtOAc (Org-2)	2.6	0.003	unknown
Aqueous-2	1.4	0.001	unknown
EtOAc (Org-3)	4.1	0.004	unknown
Aqueous-3	15.9	0.017	8 single unknowns at 0.5-4.9%, 1.9% (0.002 ppm) multiple unknowns
Residue	7.7	0.008	
"TP"(0.154 ppm)			
ACN/water	64.3	0.099	
Hexane	1.7	0.003	
EtOAc (Org-1)	45.3	0.070	37.6% (0.058 ppm) XDE-564, 4.6% (0.007 ppm) ASTP, 6 single unknowns at 0.1-0.9%
Aqueous-1	2.7	0.004	
Insoluble			subjected to aqueous acetone extraction, buffer rinse, enzyme and acid treatments
EtOAc (Org-2)	3.7	0.006	
Aqueous-2	2.7	0.004	
EtOAc (Org-3)	4.8	0.007	
Aqueous-3	17.2	0.026	>11 single unknowns at 0.4-6.2%
Residue	8.0	0.012	

Conclusion: The nature of diclosulam in the ruminant is adequately understood. Only kidney and liver were analyzed for metabolites. Diclosulam and its 5-hydroxy metabolite (5-OH-XDE-564) were identified in these two tissues. In liver, diclosulam accounted for 19% TRR (0.014 ppm) from the aniline label and 17.9% TRR (0.008 ppm) from the triazolopyrimidine label, and its 5-hydroxy metabolite accounted for 18.2% TRR (0.014 ppm) from the aniline label and 13.1% TRR (0.007 ppm) from the triazolopyrimidine label. In kidney, diclosulam was the major residue identified at 48% TRR (0.052 ppm) from the aniline label and 37.6% TRR (0.058 ppm) from the triazolopyrimidine label. Also determined was a minor metabolite, 5-ethoxy-7-fluoro[1,2,4]triazolo[1,5-c]pyrimidine-2-sulfonamide (ASTP, 4.6% TRR, 0.007 ppm) in kidney from the triazolopyrimidine label.

Poultry

44103505 Wright, J.; Collins, R. (1996) Nature of Residues of (carbon 14)XDE-564 in Laying Hen: Lab Project Number: MET94038: 41567. Unpublished study prepared by ABC Labs, Inc. and DowElanco. 209 pp

DowElanco submitted data depicting the metabolism of [aniline-UL-^{14}C]diclosulam and [triazolopyrimidin-7,9-^{14}C]diclosulam by hens following multiple oral doses. The in-life phase of the study and determination of total radioactive residues in tissues, egg, and excreta were conducted by ABC Laboratories, Columbia, MO. The analytical phase was conducted by the petitioner's North American Environmental Chemistry Laboratory at Indianapolis, IN.

The test substance uniformly labeled on the aniline ring had a specific activity of 59.6 µCi/mg and a radiochemical purity of 99.3%. The test substance labeled at positions 7 and 9 on the triazolopyrimidine rings had specific activity of 57.4 µCi/mg and a radiochemical purity of 98.5%. For dosing, both ^{14}C-labels were diluted with non-radiolabeled diclosulam to final specific activities of 38,000 dpm/μg (aniline-^{14}C) and 39,400 dpm/μg (TP-7,9-^{14}C).

Two groups of ten hens were dosed orally twice daily with [aniline-^{14}C] or [T,P-7,9-^{14}C]diclosulam for five consecutive days via capsule at mean doses of 1.18 and 1.21 mg/hen/day, respectively. Based on average feed consumption for the dosing period, these dose levels are respectively equivalent to 10.2 and 10.3 ppm of diclosulam in the diet, equivalent to ~1000x the maximum theoretical dietary exposure of 0.01 ppm for poultry.

Eggs were collected twice daily. Eggs collected in the evening were refrigerated overnight and composited with eggs collected the following morning. Excreta were collected daily prior to the morning dosing. The animals were sacrificed 20-22 hours after the last dose, and composite muscle (dark and light meat), abdominal fat, skin, and liver were collected. Samples were composited by dose groups and stored at ~-20 C until analysis.

Samples of tissue (excluding fat), eggs, and excreta were radioassayed in triplicate by combustion/LSC. Fat samples were solubilized and radioactivity determined in triplicate by direct LSC. The LOQs for the radioassays were 0.0016-0.0028 ppm for eggs and tissue. The total dosed radioactivity recovered was 77.1 and 90.6% for [aniline-^{14}C] and [TP-7,9-^{14}C]diclosulam, respectively, of which 76.9 and 90.2% of the administered dose was excreted. Radioactivity in eggs (0.04%) and tissues (0.21-0.22%) together accounted for ~0.3%.

The TRR in eggs and edible tissues are summarized in Table 7. ^{14}C-Residues in eggs increased throughout the dosing period, peaking on Day-5 at 0.022-0.023 ppm. ^{14}C-Residues were 0.022 ppm in eggs collected from [aniline-^{14}C]diclosulam hens during the 0.5 day interval preceding sacrifice. The concentrations of ^{14}C-residues in tissues were similar for both ^{14}C-labels, and were higher in skin (0.224-0.225 ppm) and liver (0.179-0.193 ppm), and lower in fat (0.011-0.014 ppm) and muscle (0.026-0.035 ppm).

Table 7. Total radioactive residues in eggs and edible tissues of hens dosed for 5 days with [aniline-UL-^{14}C] or [triazolopyrimidine-7,9-^{14}C]diclosulam at ~10 ppm/day. [a]

Matrix	Sampling Interval (Study Day)	Total Radioactive Residues (ppm) [b]	
		[Aniline-UL-^{14}C]	[Triazolopyrimidine-7,9-^{14}C]
Egg	1	0.002	0.002
	2	0.002	0.006
	3	0.009	0.011
	4	0.013	0.015
	5	0.022	0.023
Muscle (composite)	5	0.026	0.035
Skin		0.224	0.225
Fat (abdominal)		0.014	0.011
Liver		0.193	0.179

[a] Equivalent to ~1000x the maximum theoretical dietary burden for poultry.

[b] Expressed in [^{14}C]diclosulam equivalents; data are the means of triplicate analyses of pooled samples from 10 hens per dose group.

Skin and fat. ^{14}C-residues in skin and fat were extracted twice with acetonitrile (ACN):water (8:2, v/v) and filtered. ^{14}C-residues in the initial extract were partitioned with hexane, acidified (pH 2.0), and then partitioned with ethyl acetate (EtOAc). Radioactivity in the EtOAc extract was analyzed by HPLC and TLC. Unextracted ^{14}C-residues accounted for ~10% of the TRR (0.022-0.023 ppm) in skin, and ~13% of the TRR (0.002 ppm) in fat, and were not further analyzed.

Liver and Muscle. ^{14}C-residues in liver and muscle were extracted twice with ACN:H_2O (80:20, v/v) and filtered. Solubilized ^{14}C-residues were partitioned with hexane, acidified (pH 2.0), and partitioned with EtOAc. EtOAc-soluble residues were then partitioned between water and dichloromethane (DCM). Radioactivity in the DCM extract was analyzed by HPLC and TLC. The DCM fraction was further separated by anion exchange and/or silica gel SPE chromatography, and subsequent HPLC/TLC analyses of the purified ^{14}C-residues confirmed the results of the initial analyses.

Unextracted ^{14}C-residues in muscle were insignificant (15-28%TRR, 0.004-0.010 ppm) and were not further analyzed. However, unextracted radioactivity in liver accounted for 54.5-62.5%TRR (0.098-0.121 ppm), and was further investigated. The ^{14}C-residues were extracted by shaking overnight in 0.05 M Tris buffer (pH 7.5) at 37 C, centrifuged, and decanted. The unextracted radioactivity was digested using Pronase E in 0.05 M Tris buffer (pH 7.5) at 37 C overnight, and the remaining insoluble portion was hydrolyzed with 2 N HCl under reflux for 2 hours. Buffer extraction, enzyme digestion, and acid hydrolysis succeeded in releasing respectively 11.8-15.7%TRR (0.023-0.028 ppm), 32.8-42.2%TRR (0.059-0.081ppm), and 2.7-5.5% (0.005-0.011

ppm) or a total of 51.2-59.5% of the TRR; ≤2.4% of the TRR (≤0.005 ppm) remained unextracted.

^{14}C-residues in the enzyme hydrolysate were precipitated with acetic acid, partitioned with EtOAc (precipitating minor amounts of radioactivity), and then partitioned between DCM and water. The aqueous fraction contained the only significant levels of radioactivity (19.8-29.3%TRR, 0.036-0.057 ppm), and was further fractionated using an XAD-4 column eluted sequentially with water, MeOH:H_2O (5:95, v/v), MeOH:H_2O (10:80, v/v), MeOH:H_2O (25:75, v/v), MeOH:H_2O (50:50, v/v), MeOH:H_2O (75:25, v/v), 100% MeOH, and EtOAc. Each of the XAD-4 eluants contained ≤2.5% of the TRR (≤0.004 ppm) with the exception of the 100% water fractions which contained 6.2-11.1% of the TRR (≤0.021 ppm). Reverse phase (RP) HPLC analysis of the water fraction and the combined 75-100% methanolic fractions (0.006-0.008 ppm) indicated that these fractions contained multiple components (7-13 peaks), each containing minor amounts of radioactivity. The largest single component was an early-eluting peak found in the [aniline-^{14}C]diclosulam water fraction, accounting for 2.4% of the TRR (0.005 ppm).

Egg. ^{14}C-residues in eggs were extracted twice with ACN:H_2O (80:20, v/v) and filtered. The ^{14}C-residues were partitioned with hexane, acidified to pH 2.0, and then partitioned with EtOAc. The EtOAc-soluble residues were then partitioned between water and DCM. ^{14}C-Residues in the DCM extract were analyzed by HPLC and TLC. The DCM fraction was separated on a reverse phase C_{18} SPE column (eluted with varying concentrations of water to ACN) into multiple fractions each containing minor amounts of radioactivity that were not further analyzed. Unextracted ^{14}C-residues accounted for <0.01 ppm and were not further analyzed.

The distribution of radioactivity following the extraction of residues from eggs and poultry tissues is presented in Tables 8 and 9.

Table 8. Distribution of radioactivity following extraction of residues from eggs and tissues of hens dosed for 5 days with [aniline-UL-^{14}C] diclosulam at ~10 ppm/day (~500x the maximum theoretical dietary burden for poultry).

[Aniline-UL-^{14}C]diclosulam										
Fraction	Egg (0.022 ppm) [a]		Liver (0.193 ppm)		Muscle (0.026 ppm)		Skin (0.224 ppm)		Fat (0.014 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
ACN/H_2O	55.1	0.012	38.2	0.074	72.4	0.019	91.8	0.206	98.3	0.014
Hexane	0.4	<0.001	0.1	<0.001	0.2	<0.001	0.1	<0.001	9.5	0.001
EtOAc	46.1	0.010	35.5	0.069	72.8	0.019	84.6	0.190 [b]	108.6	0.015 [b]
DCM	50.0	0.011 [b]	32.0	0.062 [b]	72.8	0.019 [b]	NA	NA	NA	NA
Aqueous-2	0.9	<0.001	3.0	0.006	0.6	<0.001	NA	NA	NA	NA
Aqueous-1	0.9	<0.001	1.8	0.003	--	ND [d]	--	ND	--	ND
Post-extraction Solids	28.6	0.006	62.5	0.121	15.1	0.004	9.8	0.022	13.7	0.002
Buffer soluble	NA [c]		11.8	0.023	NA		NA		NA	
Enzyme (Pronase E)			42.2	0.081						
Acid precipitate			0.1	<0.001						
EtOAc precipitate			5.1	0.010						
DCM			2.7	0.005						
Aqueous			29.3	0.057 [e]						
2 N HCl			5.5	0.011						
Unextracted	28.6	0.006	2.4	0.005	15.1	0.004	9.8	0.022	13.7	0.002

[a] TRR are for composite samples from the 10 hens in each group. Eggs collected on Day-5 were used. Percent TRRs not corrected for percent recovery.
[b] Fraction analyzed by HPLC/TLC.
[c] NA = Not applicable; fraction not obtained from this matrix.
[d] ND = No radioactivity detected in the fraction.
[e] Separated by XAD-4 chromatography into multiple fractions containing minor amounts of radioactivity (≤0.003 ppm, except polar ^{14}C-residues in the 100% water rinse at 0.021 ppm). RP-HPLC analysis indicated the water fraction contained multiple components (8 peaks) each at ≤2.4%TRR (≤0.005 ppm).

Table 9. Distribution of radioactivity following extraction of residues from eggs and tissues of hens dosed for 5 days with [triazolopyrimidin-7,9-^{14}C]diclosulam at ~10 ppm/day (~500x the maximum theoretical dietary burden for poultry).

[triazolopyrimidine-7,9-^{14}C]diclosulam										
Fraction	Egg (0.023 ppm) [a]		Liver (0.179 ppm)		Muscle (0.035 ppm)		Skin (0.225 ppm)		Fat (0.011 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
ACN/H_2O	58.2	0.013	47.7	0.085	79.0	0.028	92.1	0.207	132.8	0.015
Hexane	0.2	<0.001	<0.1	<0.001	0.5	<0.001	<0.1	<0.001	--	ND
EtOAc	60.2	0.014	44.2	0.079	76.3	0.027	89.7	0.202 [b]	76.6	0.008 [b]
DCM	50.1	0.012 [b]	39.5	0.071 [b]	68.7	0.024 [b]	NA	NA	NA	NA
Aqueous-2	1.5	<0.001	2.6	0.005	1.5	0.001	NA	NA	NA	NA
Aqueous-1	1.8	<0.001	1.9	0.003	0.4	<0.001	0.1	<0.001	--	ND
Post-extraction Solids	21.8	0.005	54.5	0.098	28.0	0.010	10.2	0.023	11.5	0.002
Buffer soluble	NA[c]		15.7	0.028	NA		NA		NA	
Enzyme (Pronase E)			32.8	0.059						
Acid precipitate			0.1	<0.001						
EtOAc precipitate			4.2	0.008						
DCM			3.9	0.007						
Aqueous			19.8	0.036 [e]						
2 N HCl			2.7	0.005						
Unextracted	21.8	0.005	0.6	0.001	28.0	0.010	10.2	0.023	11.5	0.002

[a] TRR are for composite samples from the 10 hens in each group. Eggs collected on Day-5 were used.

[b] Fraction analyzed by HPLC/TLC.

[c] NA = Not applicable; fraction not obtained from this matrix.

[d] ND = No radioactivity detected in the fraction

[e] Separated by XAD-4 chromatography into multiple fractions containing minor amounts of radioactivity (≤0.004 ppm, except polar ^{14}C-residues in the 100% water rinse at 0.011 ppm). RP-HPLC analysis indicated the water fraction contained multiple components (7 peaks) each at ≤1.9%TRR (≤0.003 ppm).

Radioactive residues in solvent extracts and fractions were analyzed by HPLC using a reverse-phase column with a linear gradient of water:acetic acid:triethyl amine (98.9:1.0:0.1, v/v) to ACN (98.9:1.0:0.1, v/v). ^{14}C-Residues were detected using an in-line radioactivity detector and by LSC of collected fractions; unlabeled reference compounds were detected using a UV absorbance detector, with detection typically set at 250 nm. A total of 4 reference standards including parent, TPSA (5-ethoxy-7-fluoro-1,2,4-triazolo[1,5-c]pyrimidine-2-sulfonic acid), ASTP, and 5-hydroxy-diclosulam were used for comparison. Confirmation of metabolites identified by HPLC was obtained by co-chromatography using 1D-TLC on Merck Kieselgel 60 F_{254} plates using a solvent system consisting of toluene:ACN:water (50:45:5, v/v). ^{14}C-residues were detected and quantified using a Berthold 484 Linear Analyzer, and reference compounds were detected using UV light.

Confirmation of the identity of parent compound isolated from excreta of hens (both labels) and a hydroxylated metabolite of diclosulam isolated from excreta of [aniline-^{14}C]diclosulam-treated hens was obtained by MS analyses of the isolated metabolites. The exact position of the hydroxy group on the phenyl ring was not established. Based on the retention times determined for the metabolite found in excreta, trace amounts of the hydroxyphenyl metabolite were detected in each poultry matrix for both labels; concentrations were highest in skin at 3.0% of the TRR (0.007 ppm). As the presence of the hydroxyphenyl metabolite was not confirmed by co-chromatography against a reference standard, the identification of the metabolite in poultry tissue and eggs is considered tentative.

Summaries of the identification/characterization of ^{14}C-residues in tissues and egg from hens dosed with [aniline-UL-^{14}C]- or [TP-7,9-^{14}C]diclosulam are presented in Tables 10 and 11, respectively. The chemical names and structures of diclosulam and its metabolites in plants and animals are depicted in Attachment 1 (Figure A).

The metabolic patterns of the two [^{14}C]diclosulam test substances were qualitatively and quantitatively similar. Parent diclosulam was the principle component of the residue, accounting for 23-27% of the TRR (0.042-0.053 ppm) in liver; 50-66% of the TRR (0.017 ppm) in muscle; 79-88% of the TRR (0.178-0.199 ppm) in skin; 62-94% of the TRR (0.006-0.013 ppm) in fat, and 35-37% of the TRR (0.008 ppm) in eggs. The sulfonamide bridge cleavage product, 5-ethoxy-7-fluoro-(1,2,4)triazolo[1,5-c]pyrimidine-2-sulfonamide (ASTP), accounted for 8.3-17.6% (0.002-0.023 ppm) in [TP-7,9-^{14}C]diclosulam-labeled liver, muscle, and eggs. Trace amounts of a putative hydroxyphenyl diclosulam metabolite were also found in all hen matrices at ≤3% of the TRR (≤0.007 ppm).

After collection and preparation for analysis, samples of tissue and eggs were stored at ~-20 C for up to one week at ABC Laboratories until shipment to DowElanco by overnight carrier on dry ice. Samples were stored frozen (~-20 C) at DowElanco prior to analysis. The petitioner states that all tissue samples were extracted and an initial characterization conducted within 4 months of sacrifice; egg and excreta samples were stored for up to 7 months prior to extraction and initial analysis. The data package also indicates that work-ups on the post-extraction solids

were not begun until 7 months after collection. The petitioner did not indicate when the definitive sample analyses were completed, although the experimental termination date was 16.4 months after sacrifice. In addition, no data were provided indicating the storage stability of [^{14}C]diclosulam residues in poultry tissue or eggs.

Conclusion: Provided that residues of diclosulam are stable in poultry egg and tissues under frozen storage, the nature of diclosulam in poultry is adequately understood. The petitioner must clarify the storage time between sampling and analysis for poultry and eggs in the metabolism study; if the storage time was longer than 6 months, evidence should be provided that the identity of residues had not changed during this period between collection and final analysis. Overall, >73% of the TRR in tissues and 50-60% in eggs was adequately identified or characterized. The metabolic patterns of the two [^{14}C]diclosulam test substances were qualitatively and quantitatively similar. Parent diclosulam was the principle component of the residue, accounting for 23-27% of the TRR (0.042-0.053 ppm) in liver; 50-66% of the TRR (0.017 ppm) in muscle; 79-88% of the TRR (0.178-0.199 ppm) in skin; 62-94% of the TRR (0.006-0.013 ppm) in fat, and 35-37% of the TRR (0.008 ppm) in eggs. The sulfonamide bridge cleavage product, ASTP, accounted for 8.3-17.6% (0.002-0.023 ppm) in [TP-7,9-^{14}C]diclosulam-labeled liver, muscle, and eggs. Trace amounts of a putative hydroxyphenyl diclosulam metabolite were also found in all hen matrices at ≤3% of the TRR (≤0.007 ppm).

Table 10. Characterization and identification of ^{14}C-residues in eggs and tissues from hens dosed with **[aniline-UL-^{14}C]**diclosulam at ~10 ppm/day (~500x the maximum theoretical dietary burden).

Component	Liver (0.193 ppm)		Muscle (0.026 ppm)		Skin (0.224 ppm)		Fat (0.014 ppm)		Egg (0.022 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Diclosulam	27.2	0.053	66.2	0.017	79.3	0.178	94.2	0.013	37.3	0.008
Total identified	**27.2**	**0.053**	**66.2**	**0.017**	**79.3**	**0.178**	**94.2**	**0.013**	**37.3**	**0.008**
Unknown HPLC Peaks [b]	4.9	0.010	6.4	0.002	4.9	0.011	14.3	0.002	11.9	0.002
Aqueous	4.8	0.009	0.6	<0.001	--	ND [a]	--	ND	1.8	<0.001
Non-extractable	62.5	0.121	15.1	0.004	9.8	0.022	13.7	0.002	28.6	0.006
Buffer soluble	11.8	0.023	Not Applicable							
Enzyme Released Acid precipitate	0.1	<0.001								
EtOAC precipitate	5.1	0.010								
Organosoluble	2.7	0.005								
Aqueous	29.3	0.057[c]								
2N HCl	5.5	0.011								
Total identified or characterized	**91.4**	**0.176**	**73.2**	**0.019**	**84.2**	**0.189**	**108.5**	**0.015**	**51.0**	**0.011**
Unextracted	2.4	0.005	15.1	0.004	9.8	0.022	13.7	0.002	28.6	0.006

[a] ND = not detected.

[b] Consists of 2-8 unknown peaks including a putative hydroxyphenyl-diclosulam metabolite (each@ ≤0.007 ppm).

[c] Further fractionation by XAD-4 chromatography yielded eight fractions, each containing ≤1.5% of the TRR with the exception of the water eluate which contained 11.1% of the TRR (≤0.021 ppm). RP-HPLC analysis indicated that the water fraction contained multiple components (8 peaks) each at ≤2.4%TRR (≤0.005 ppm).

Table 11. Characterization and identification of ^{14}C-residues in eggs and tissues from hens dosed with **[triazolopyrimidine-7,9-^{14}C]**diclosulam at ~10 ppm/day (~500x the maximum theoretical dietary burden).

Component	Liver (0.179 ppm)		Muscle (0.035 ppm)		Skin (0.225 ppm)		Fat (0.011 ppm)		Egg (0.023 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Diclosulam	23.2	0.042	49.5	0.017	88.4	0.199	61.7	0.006	34.5	0.008
ASTP [a]	12.6	0.023	17.6	0.006	ND [b]	--	ND	--	8.3	0.002
Total identified	**35.8**	**0.065**	**67.1**	**0.023**	**88.4**	**0.199**	**61.7**	**0.006**	**42.8**	**0.010**
Unknown HPLC Peaks [c]	3.7	0.007	18.3	0.007	1.3	0.003	14.8	0.001	15.0	0.004
Aqueous	4.5	0.008	1.9	<0.001	0.1	<0.001	0.1	<0.001	2.3	<0.001
Non-extractable	54.5	0.098	28.0	0.010	10.2	0.023	11.5	0.002	21.8	0.005
Buffer soluble	15.7	0.028	Not Applicable							
Enzyme released Acid precipitate	0.1	<0.001								
EtOAC precipitate	4.2	0.008								
Organosoluble	3.9	0.007								
Aqueous	19.8	0.036 [d]								
2N HCl	2.7	0.005								
Total identified or characterized	**90.4**	**0.162**	**87.3**	**0.031**	**89.8**	**0.202**	**76.6**	**0.008**	**60.1**	**0.014**
Unextracted	0.6	0.001	28.0	0.010	10.2	0.023	11.5	0.002	21.8	0.005

[a] Identified in liver extracts by co-chromatography with reference standards, and tentatively detected in muscle and egg by 1-D TLC based on R_f values.

[b] ND = not detected.

[c] Includes 4-8 unknown peaks including a putative hydroxyphenyl-diclosulam metabolite (each @≤0.003 ppm).

[d] Further separation by XAD-4 chromatography yielded eight fractions, each containing ≤2.5% of the TRR with the exception of the water eluate which contained 6.2% of the TRR (0.011 ppm). RP-HPLC analysis indicated that the water fraction contained multiple components (7 peaks) each at ≤1.9%TRR (≤0.003 ppm).

The HED Metabolism Assessment Review Committee discussed the metabolism of diclosulam in plants and livestock and concluded that finite transfer of diclosulam residues to meat, milk, poultry and eggs is not expected as a result of the proposed use (MARC memo of 12-6-99, L. Cheng). Tolerances in livestock and feeding studies are not required as a result of the proposed use. The Committee also concluded that should feeding studies be necessary in the future, diclosulam should be determined. Furthermore, for dietary exposure assessment in ruminant liver, the level of diclosulam will be doubled to account for 5-hydroxy diclosulam.

OPPTS GLN 860.1340: Analytical Methods

The method for analyzing residues of diclosulam in peanut nutmeat, hay, meal, and oil is coded GRM 96.01, "Determination of Residues of Diclosulam in Peanut Nutmeat, Hay, Meal, and Refined Oil by Capillary Gas Chromatography with Mass Selective Detection", dated July 17, 1996 (MRID 44315103).

Briefly, samples of peanut nutmeat, hay or meal are extracted by blending with acetone. An aliquot of the extract is filtered, evaporated to dryness, and the remaining residue is buffered to pH 7 with potassium dihydrogen phosphate. For peanut nutmeat, the aqueous buffer solution is additionally partitioned against isooctane to remove oils. The buffer solution is filtered prior to acidification with 2N hydrochloric acid for nutmeat or meal and filtered after acidification for hay. For peanut refined oil, it is dissolved in hexane and partitioned against pH 7 aqueous buffer solution. The aqueous buffer solution is acidified with 2N hydrochloric acid. Samples are further purified using C_{18} solid phase extraction. The eluant from the C_{18} extraction is evaporated to dryness, and the residue is dissolved in acetone and derivatized with trimethylsilyl-diazomethane under acidic conditions. Following derivatization, samples are evaporated to dryness and redissolved in water, and N-methyl-diclosulam is partitioned into toluene containing N-ethyl-diclosulam as a marker. A portion of the toluene extract is analyzed by capillary gas chromatography with mass selective detection. Ions monitored are *m/z* 174 (quantitation) and 176 (confirmation) for N-methyl compound and 188 for the marker compound. A calibration curve is constructed by plotting the quantitation ratio (*m/z* 174/*m/z* 188) versus concentration of a series of the standards. The validated limit of quantition (LOQ) is 0.01 ppm.

The method for analyzing residues of diclosulam in soybean grain, forage, and hay is coded GRM 94.19, "Determination of Residues of XDE-564 in Soybean Grain, Forage and Hay by Capillary Chromatography with Mass Selective Detection", dated February 14, 1995 (MRID 44103507); the method for soybean meal, hull and crude and refined oil is coded GRM 94.19.S1 (MRID 44103510), a supplement to GRM 94.19, dated February 28, 1995. GRM 94.19 and its supplement are essentially identical to GRM 96.01.

In GRM 94.19 and 94.19.S1, the sample (except for oil) is ground and residues of diclosulam are extracted using 9:1 acetone:0.1N hydrochloric acid. An aliquot of the extract is evaporated to dryness and the remaining residue is buffered at pH 7. For soybean crude and refined oil,

diclosulam residues are extracted with hexane and partitioned against a pH 7 buffer solution. The aqueous buffer solutions are acidified with 2N hydrochloric acid, heated, then cooled to ambient temperature, filtered (for soybean grain, forage, hay, meal, and hull) and purified using C_{18} solid phase extraction. The remainder of the procedure is identical to GRM 96.01. The limit of quantitation for all the soybean matrices tested are 0.01 ppm.

Table 12. Results of Method Validation

Commodity	Fortification Level (ppm)	% Recovery
Peanut nutmeat	0.010	82, 89, 74, 83, 86, 86, 85, 85, 92 mean=85
	0.10	79, 81, 78, 76 mean=78
Peanut hay	0.010	93, 84, 97, 74, 89, 92, 81, 88 mean=87
	0.10	76, 77, 79, 77, 73 mean=77
Peanut meal	0.010	74, 84, 86, 76, 82, 83, 78, 78, 78, 74 mean=79
	0.10	78, 76, 80, 74, 75 mean=77
Peanut refined oil	0.010	106, 103, 102, 99, 105, 102, 99, 102, 102, 101 mean=100
	0.10	83, 100, 86, 86, 104, 101 mean=94
Soybean grain	0.010	85, 80, 85, 92, 88, 89, 88, 86 mean=87
	0.020	81, 82, 84 mean=82
	0.050	75, 68, 79 mean=74
	0.10	76, 77, 78 mean=77
Soybean forage	0.010	97, 96, 98, 97, 96, 96, 100, 94 mean=97
	0.020	90, 91, 91 mean=91

Commodity	Fortification Level (ppm)	% Recovery
	0.050	83, 88, 88 mean=86
	0.10	80, 84, 84 mean=83
Soybean hay	0.010	92, 94, 95, 99, 94, 91, 91, 96 mean=94
	0.020	90, 89, 85 mean=88
	0.050	86, 84, 86 mean=85
	0.10	79, 79, 77 mean=78
Soybean meal	0.010	85, 92, 83, 84, 91, 91, 93, 92 mean=89
	0.020	97, 73, 96 mean=89
	0.050	88, 90, 91 mean=90
	0.10	85, 86, 86 mean=86
Soybean hull	0.010	82, 79, 79, 84, 79, 84, 86, 91 mean=83
	0.020	97, 96, 99 mean=97
	0.050	90, 91, 88 mean=90
	0.10	79, 79, 76 mean=78
Soybean crude oil	0.010	113, 110, 118, 113, 112, 113, 117, 119 mean=114
	0.020	88, 92, 104 mean=95
	0.050	94, 96, 85 mean=92
	0.10	79, 78, 90 mean=82

Commodity	Fortification Level (ppm)	% Recovery
Soybean refined oil	0.010	82, 81, 84, 86, 82, 88, 92, 89 mean=86
	0.020	90, 91, 92 mean=91
	0.050	89, 92, 92 mean=91
	0.10	80, 88, 85 mean=84

Independent laboratory validation

The petitioner submitted method validation data using GRM 96.01 for peanut commodities and GRM 94.19 for soybean commodities. These methods have been proposed as enforcement methods.

The independent laboratory validation (MRID 443151-01 & -02) was conducted by the Environmental Fate and Residue Chemistry group of Dow AgroSciences and Quality Management & Analytical Services, Inc, Walhalla, ND. The registrant emphasized that the validation of GRM 96.01 was conducted in a group that had no previous experience with diclosulam and no prior knowledge of the residue methodology for the analyte. Further, no contact was permitted between the method testing group and the method development group before the first method trial, and except for the mass selective detector, entirely different equipment and supplies were used.

For peanut, samples (2 control and 3 fortified for each matrix) of untreated peanut nutmeat and hay were fortified with 0.010 ppm and 0.020 ppm diclosulam and analyzed by the testing laboratory using GRM 96.01. Both intial trials yielded acceptable recoveries: 89-98% at 0.010 ppm and 89-96% at 0.020 ppm for peanut nutmeat and 81-86% at 0.010 ppm and 74-79% at 0.020 ppm for peanut hay. For soybean, samples (2 control and 2 fortified for each matrix) of untreated soybean grain, forage, and hay were fortified with 0.010 and 0.050 ppm diclosulam were tested using GRM 94.19. The method yielded acceptable recoveries for soybean grain (102 and 104% at 0.010 ppm; 92 and 94% at 0.050 ppm) and soybean forage (89 and 113% at 0.010 ppm; 74 and 71% 0.050 ppm). Untreated soybean hay was found to be contaminated with an interfering component present at 0.0024-0.0030 ppm. By correcting for the background contamination, diclosulam was recovered at 98 and 105% at 0.010 ppm and 85 and 86% at 0.050 ppm) in soybean hay. A set of 9 peanut samples took about 2 calendar days to complete.

Conclusion: The method validation conducted using peanut matrices is sufficient to demonstrate the applicability of GRM 96.01 and 94.19 as enforcement methods. The registrant is required to submit a sample each of diclosulam, N-methyl diclosulam and N-ethyl diclosulam. A

radiovalidation study in plant matrices is not required for this petition since none of the plant metabolism samples contained quantifiable diclosulam. A radiovalidation study in livestock matrices is also not required since livestock tolerances are not required for this petition. However, for future uses on crops in which finite levels of diclosulam occur in plants and livestock, radiovalidation studies will be needed as stated 860.1340.

Pesticide interference study

The interference study was conducted for GRM 94.19, 94.19.S1, and 96.01 (plus GRM 94.07.R1, 94.09, and 96.01.S1) on other commonly used pesticides. Of the 58 compounds studied, none were found to interfere with diclosulam. Two chemicals, esfenvalerate and flumetsulam, eluted at retention times that were very close to diclosulam but were ruled out by their mass spectra.

GLN 860.1360: Multiresidue Method

The petitioner submitted data concerning the recovery of residues of diclosulam using FDA multiresidue method protocols (PAM Vol 1). The data have been forwarded to FDA for evaluation.

> 44103503 Conrath, B.A. and L. Atkin (1995) Behavior of XDE-564 in Multi-Residue Method Testing Using Methods Outlined in FDA Pesticide Analytical Manual Volume I (PAM-I): Study ID RES95047. Unpublished study prepared by DowElanco and ABC Laboratories, Inc. 47 pp

Diclosulam was recovered through Protocol C. The compound was not recovered from Protocol D, E, F due to its lack of mobility on the Florisil column, and in the case of Protocol D, the lack of sensitivity of the detector to diclosulam. Protocol A and B are not applicable to diclosulam.

OPPTS GLN 860.1380: Storage Stability Data - Plants

DowElanco submitted the following data depicting the frozen storage stability of residues of diclosulam in/on soybean seed, forage, and hay:

> 44103511 Robb, C. (1996) Frozen Storage Stability of XDE-564 in Soybean Grain, Forage, and Hay: Lab Project Number: RES94153. Unpublished study prepared by DowElanco North American Environmental Chemistry Lab. 66 pp

On the day of preparation (Day-0), a single control, two freshly-fortified controls, and five stored-fortified samples of soybean seed, forage, and hay were analyzed; at each subsequent sampling interval (41-57, 80-96, 210-226, 367-383 days), three stored-fortified samples were analyzed. The fortified samples (spiked with diclosulam at 0.1 ppm each) and unfortified control samples were stored frozen at ~-20 C. Samples were analyzed for residues of diclosulam

using DowElanco method GRM 94.19. As low recoveries were obtained from stored-fortified seed samples on the day of preparation, the method was modified to include a hexane partition step to remove excessive oil prior to C_{18} SPE clean-up; the petitioner reported the results of the reanalysis which occurred 16 days after fortification as the time-zero analysis.

Apparent residues of diclosulam were <0.01 ppm (<LOQ) in/on five control samples each of seed, forage, and hay. Adequate concurrent recoveries of diclosulam were obtained; overall recoveries were 71-87% from 10 samples of seed, forage, and hay freshly-fortified with diclosulam at 0.1 ppm. Sample analyses were conducted by DowElanco at their North American Environmental Chemistry Laboratory (Indianapolis, IN). Adequate representative chromatograms and sample calculations were provided.

The results of the storage stability studies are presented in Table 13. The submitted data indicate that residues of diclosulam are stable at ~-20 C in soybean seed, forage, and hay for up to 1 year.

Table 13. Stability of diclosulam fortified in soybean matrices at 0.1 ppm and stored at ≤-20 C for up to 1 year.

Commodity	Storage Interval (Days)	Fresh Fortification % Recovery [a]	Stored Samples % Recovery (uncorrected)	Average Corrected % Recovery [b]
Seed	16	75, 78 (77)	78, 72, 76, 72, 74	--
	41	87, 84 (86)	75, 69, 73	84
	80	81, 80 (80)	60, 64, 65	79
	210	85, 85 (85)	72, 68, 67	82
	367	83, 82 (82)	65, 69	82
Forage	0	76, 75 (76)	81, 84, 83, 84, 82	--
	57	83, 83 (83)	84, 87, 85	102
	96	78 (78)	80, 81, 82	105
	226	81, 76 (78)	77, 77, 68	94
	383	82, 84 (83)	79, 76, 81	95
Hay	0	71, 71 (71)	76, 74, 77, 74, 76	--
	57	81, 77 (79)	76, 77, 77	97
	96	78, 75 (77)	75, 74, 76	98
	226	73, 78 (76)	77, 74, 72	98
	383	74, 78 (76)	72, 74	97

[a] Value in parentheses represents the average recovery from freshly-fortified control samples.
[b] Average of three stored-fortified recoveries each corrected for the average fresh-fortification recovery.

Conclusions: The submitted storage stability study on diclosulam is adequate and indicates that residues of diclosulam *per se* are stable at ~- 20 C in soybean seed, forage, and hay for up to 1

year. Samples from the submitted residue studies on peanuts and soybeans were stored frozen for a maximum of 39 days or 8 months, respectively, from collection to analysis. The storage intervals and conditions of the residue studies are adequately supported by the storage intervals depicted in the available storage stability study.

OPPTS GLN 860.1500: Crop Field Trials

Soybeans

DowElanco submitted data (citations shown below) from 24 field trials conducted during 1994 and 1995 in AR (2), GA, IA (2), IL (2), IN (2), KS, KY, LA, MI, MN, MO (2), MS, NC, ND, NE, OH, SD, VA, and WI depicting residues of diclosulam in/on soybean commodities.

> 44103512 Stafford, L.; Schwake, J.; Robb, C.; et al. (1996) Magnitude of the Residues of XDE-564 in Soybean Grain Following Preplant Incorporated and Preemergence Applications and in Soybean Grain Processed Fractions Following Preemergence Application: Lab Project Number: RES95019: 01BF309IL: 02BF309IL. Unpublished study prepared by DowElanco. 185 pp
>
> 44103513 Rutherford, B.; Robb, C. (1996) Magnitude of Residues of XDE-564 Herbicide in Soybeans Following Preplant Incorporation and in Soybean Processed Fractions Following Preemergence Application: Lab Project Number: RES94005: SYB9401: SYB9402. Unpublished study prepared by DowElanco North American Environmental Chemistry Lab. 132 pp

1994 Soybean Trials (MRID 44103513)

In three crop field trials, diclosulam (83.4% DF) was applied once to soybeans preplant incorporated (PPI) 14 days prior to planting at 0.038-0.047 lb ai/A (1.2-1.5x the proposed maximum seasonal rate). Applications were made using ground equipment in 19-24 gal/A of water. Diclosulam was also applied preemergence at planting at 0.092 lb ai/A (2.9x) in one test conducted at Wayside, MS to generate samples for processing.

A single control and treated sample of soybean forage and hay were harvested at beginning pod growth to full pod elongation (R3-R4 growth stage), 83-102 days after treatment. Forage samples were placed in frozen storage within four hours of collection, and hay samples were dried in a sheltered area for 3-7 days prior to frozen storage. A single control and treated sample of soybean seed were harvested at maturity, 125-157 days after treatment, and were placed in frozen storage within 9 hours of collection. All samples were held at ~-20 C at the test facilities prior to shipment. Grain samples for processing were shipped frozen by overnight carrier to the Texas A&M University, Food Protein Research and Development Center (Bryan, TX). The remaining soybean RAC samples were shipped by overnight carrier on dry ice or ACDS freezer truck to DowElanco (Indianapolis, IN), where the samples were stored at ~-20 C prior to

analysis. The soybean RAC samples were stored frozen for up to 8 months prior to analysis (176 days for seed; 245 days for forage and hay).

Residues of diclosulam were determined using DowElanco method GRM 94.19. Adequate concurrent recoveries were obtained from control samples of seed (67-92%; $\bar{x}$ = 79±8%; n=13), forage (86-108%; $\bar{x}$ =97±8%; n=10), and hay (78-110%; $\bar{x}$ =92±10%; n=10) fortified with diclosulam at 0.01-0.1 ppm. Residues of diclosulam were below both the LOQ (0.01 ppm) and the LOD (0.003 ppm) in/on all seed, forage, and hay control samples. Residues were also <LOQ (<0.01 ppm) and <LOD (<0.003 ppm) in/on three samples each of seed, forage, and hay treated at ~1x, and <0.003 ppm (<LOD) in/on one seed sample treated at ~3x.

1995 Soybean Trials (MRID 44103512)

Diclosulam (84 % DF) was applied once to soybeans as either a preplant incorporated application (18 tests) 14-16 days prior to planting at 0.037-0.042 lb ai/A, or preemergence (21 tests) within 5 days after planting at 0.031-0.034 lb ai/A (1-1.3x the proposed rate). Applications were made using ground equipment in ~18-30 gal/A of water. In one test (Geneseo, IL), diclosulam was applied preemergence at an exaggerated rate (0.25 lb ai/A;~8x) to generate samples for processing.

A single control and duplicate treated samples of soybean seed (2-6.5 lbs each) were harvested 114-158 days after PPI application and 99-146 days after preemergence application, and were stored frozen (<-8 C) within 7 hours of collection. Seed samples for processing were shipped frozen by ACDS freezer truck to the Texas A&M University, Bryan, TX. The remaining soybean RAC samples were shipped by overnight courier on dry ice or ACDS freezer truck, or were hand-delivered on dry ice (IN tests only) to DowElanco (Indianapolis, IN), where the samples were stored at ~-20 C prior to analysis. The soybean seed RAC samples were stored frozen for up to 3 months (35-90 days) prior to analysis.

Residues of diclosulam were determined using DowElanco method GRM 94.19. Residues were <0.01 ppm (<LOQ) in/on 21 control and 78 treated (1x rate) samples of soybean seed. Residues were also <0.01 ppm in/on one soybean seed sample treated at ~8x. Adequate concurrent recoveries were obtained from seed (59-91%; $\bar{x}$ = 75±9%; n=22) fortified with diclosulam at 0.01-0.1 ppm.

Geographic representation of tests on soybeans conformed to OPPTS Series 860 guidelines, and an adequate number of samples was analyzed. Tests were conducted in Region 2 (3 tests), Region 4 (6 tests) and Region 5 (15 tests) for a total of 24 tests.

Conclusions: The submitted soybean field trial data are adequate. Residues of diclosulam were below both the LOQ (<0.01 ppm) and the LOD (<0.003 ppm) in/on all soybean seed samples (n=81) harvested 125-158 days after a single preplant incorporated or preemergence application of diclosulam (83.4 or 84.2% DF) at 0.031-0.047 lb ai/A (1-1.5x the proposed maximum

seasonal rate). Residues were also below the LOQ and LOD (<0.003 ppm) in/on three samples each of soybean forage and hay harvested 83-102 days after a single preplant incorporated treatment at 0.038-0.047 lb ai/A (1-1.5x).

The available residue data support the proposed tolerance at 0.02 ppm for residues of diclosulam in/on soybean seed. Residues were nondetectable (<0.003 ppm) in/on all 81 samples of soybeans treated at 1-1.5x. Diclosulam residues were also nondetectable (<0.003 ppm) in/on seed harvested from applications at exaggerated rates (~3 and 8x). The proposed label includes a restriction against grazing treated areas or harvesting forage and hay from treated areas; therefore, tolerances for residues in/on soybean forage and hay are not required at this time.

Peanuts

DowElanco submitted data (citation noted below) from 11 field trials conducted in AL (2), FL, GA (2), NC, OK, SC, TX (2), and VA during 1996 depicting residues of diclosulam in/on peanut nutmeat and hay.

> 44315104 McCormick, R.; Bormett, G. (1997) Magnitude of Residues of DE-564 in Peanuts: Lab Project Number: RES96005. Unpublished study prepared by DowElanco. 101 pp

Diclosulam (84.2 % DF) was applied to peanuts as a split application consisting of a preplant incorporated or preemergence application at 0.031 lb ai/A followed 81-144 days later by a postemergence application at 0.024 lb ai/A, for a total of 0.055 lb ai/A (1.4x the proposed maximum seasonal rate). Both the PPI and preemergence applications were represented at each trial location, for a total of two tests at each site. The PPI applications were made ≤5 days prior to planting, and preemergence applications were made within 3 days after planting. At two trial sites (AL-1 and GA-1), samples were collected at posttreatment intervals of 20, ~25, ~30, and 35 days to examine residue decline. Applications were made using ground equipment in 12-30 gal/A of water; for postemergence applications crop oil concentrate was added to the spray mixture at a rate of 1.25% (v/v).

Peanuts were dug and left to dry in the field for 3-11 days. A single control and treated sample of hay and peanuts harvested 16-35 days after the last application were collected and placed in frozen storage within 4 hours of sampling. The samples were shipped via FedEx overnight packed in dry ice to DowElanco, Indianapolis, IN where they were stored at ~-20 C.

Analyses for residues of diclosulam were conducted within 39 days of sampling by GC/MSD using DowElanco method GRM 96.01. Adequate concurrent recoveries were obtained from nutmeat (73-105%; $\bar{x}$ = 88 ±8%; n=20) fortified with diclosulam at 0.01-0.1 ppm, and from hay (63-135%; $\bar{x}$ = 86±16%; n=23) at the 0.01-1.0 ppm fortification levels. The method LOQ and LOD were reported as 0.01 and 0.003 ppm, respectively, for peanut nutmeats, and 0.02 and

0.006 ppm, respectively, for peanut hay. The residues were nondetectable in/on all control samples of peanut nutmeat (<0.003 ppm) and hay (<0.006 ppm).

The results of the peanut field trials are presented in Table 14. Residues of diclosulam were below both the LOQ (0.01 ppm) and LOD (0.003 ppm) in/on all 34 nutmeat samples, including residue decline samples, harvested 16-35 days after the last treatment. Residues were <0.006-0.765 ppm in/on 22 hay samples harvested 16-32 days posttreatment; residue levels were the same or slightly higher (four tests) in hay harvested from PPI- versus preemergence application. Residues were <0.006-0.010 ppm in/on 12 hay samples collected 20, 25 or 26, and 35 days posttreatment for the residue decline studies.

Geographic representation of tests on peanuts conformed to OPPTS Series 860 guidelines and an adequate number of samples was analyzed. Field trials were conducted in Region 2 (14 tests), Region 3 (2 tests), Region 6 (4 tests), and Region 8 (2 tests) for a total of 22 tests.

Conclusions: The submitted peanut field trial data are adequate. Residues of diclosulam were <0.003 ppm (<LOD) and <0.006-0.765 ppm in/on 22 samples each of peanut nutmeat and hay harvested 16-32 days after a split application of diclosulam (84.2% DF) consisting of a preplant incorporated or preemergence treatment at 0.031 lb ai/A followed 81-144 days later by a postemergence treatment at 0.024 lb ai/A, for a total of 0.055 lb ai/A (1.4x the proposed maximum seasonal rate).

The proposed label does not specify a PHI for peanuts. Based on the available data a 30-day PHI for peanuts is appropriate and should be added to the proposed label.

The available residue data support the proposed tolerance at 0.02 ppm for residues of diclosulam in/on peanut nutmeats. Residues were nondetectable (<0.003 ppm) in/on all 22 samples of nutmeats treated at 1.4x. Diclosulam residues were also nondetectable (<0.003 ppm) in/on seed harvested from applications at exaggerated rates (~3 and 8x). The proposed label includes a restriction against grazing treated areas or harvesting forage and hay from treated areas. No tolerance for residues in/on peanut hay is needed since the proposed label includes a restriction against grazing treated area or harvesting forage and hay from treated areas.

Table 14. Residues of diclosulam in/on **peanut** nutmeat and hay harvested following a split application consisting of a preplant incorporated (PPI) or preemergence (PRE) treatment at 0.031 lb ai/A followed by a postemergence treatment at 0.024 lb ai/A, for a total of ~0.055 lb ai/A (1.4x the proposed maximum seasonal rate)

Trial Location	Application data			PTI [d]	Diclosulam Residues (ppm)	
	Rate [a]	Type [b]	RTI [c]		Nutmeat	Hay
AL-1 (Grangeburg)	0.056	PPI	109	20	<0.003	(0.007) [e]
				26	<0.003	(0.009)
				31	<0.003	(0.008)
				35	<0.003	<0.006
		PRE		20	<0.003	(0.008)
				26	<0.003	(0.009)
				31	<0.003	(0.008)
				35	<0.003	(0.006)
Al-2 (Notasulga)	0.057	PPI	111	30	<0.003	(0.015)
	0.056	PRE			<0.003	(0.014)
FL (Malone)	0.055	PPI	109	31	<0.003	(0.010)
	0.056	PRE			<0.003	(0.011)
GA-1 (Meigs)	0.055	PPI	108	20	<0.003	<0.006
				25	<0.003	<0.006
				30	<0.003	(0.010)
				35	<0.003	(0.007)
		PRE		20	<0.003, <0.003 [f]	<0.006
				25	<0.003	<0.006
				30	<0.003	(0.006, 0.007)
				35	<0.003	(0.008)
GA-2 (Meigs)	0.056	PPI	95	32	<0.003	<0.006
		PRE			<0.003	<0.006
NC (Lucama)	0.056	PPI	130	16	<0.003	0.091
		PRE			<0.003, <0.003	0.079, 0.080
OK (Eakly)	0.056	PPI	110	22	<0.003	0.061
	0.055	PRE			<0.003	0.060
SC (Elko)	0.055	PPI	104	30	<0.003	0.050
		PRE			<0.003	(0.019)
TX-1 (Pattison)	0.056	PPI	81	30	<0.003	<0.006
	0.054	PRE			<0.003	<0.006
TX-2 (Levelland)	0.055	PPI	120	26	<0.003	0.765
	0.056	PRE			<0.003, <0.003	0.664, 0.634
VA (Emporia)	0.057	PPI	144	30	<0.003	0.363
	0.056	PRE	136		<0.003, <0.003	0.322, 0.308

[a] Total lbs ai/A applied.
[b] Each trial plot also received a single postemergence application.
[c] RTI = Retreatment interval in days.

[d] PTI = Posttreatment interval in days.
[e] Residue values for hay that are listed in parentheses are above the LOD (0.006 ppm) but below the LOQ (0.02 ppm).
[f] Two values indicate the results of duplicate analyses of the same sample.

OPPTS GLN 860.1520: Processed Food/Feed

Soybeans

In conjunction with the soybean field trial data (MRIDs 44103513 and 44103512), the petitioner submitted data from two soybean processing studies conducted in MS (1994) and IL (1995) in which diclosulam (83.4 and 84.0% DF) was applied to soybeans as a preemergence treatment at planting at 0.09 or 0.25 lb ai/A (~3 or 8x the proposed rate maximum seasonal rate).

A single bulk control and treated soybean seed sample (100-171 lbs) were harvested from each test 99-127 days after treatment and were stored frozen within 2 hours of collection. The samples were shipped overnight on dry ice or by ACDS freezer truck to Texas A&M University, Food Protein Research and Development Center (Bryan, TX), where the samples were processed into soybean processed fractions by simulated commercial procedures and stored frozen. The samples were then shipped overnight on dry ice to DowElanco (Indianapolis, IN) and stored at ~-20 C prior to analysis. Soybean seed (RAC) samples were stored frozen for up to 6 months from harvest to analysis, and soybean processed fractions were stored for up to 1 month from sample collection to analysis.

Residues of diclosulam were determined using GC/MSD method GRM 94.19 for seed and its supplement GRM 94.19.S1 for processed fractions. Adequate concurrent recoveries were obtained from seed (reported above) and from meal (70-99%; $\bar{x}$ =80±10%; n=9), hulls (74-98%; $\bar{x}$ = 83±9%; n=9), and crude/refined oil (62-107%; $\bar{x}$ = 92±12%; n=13) fortified with diclosulam at 0.01-0.1 ppm. Residues were <0.003 ppm (<LOD) in/on all soybean control samples. Residues of diclosulam were <0.003 ppm (<LOD) in/on two soybean seed (RAC) samples treated at ~3 or 8x and in/on the two samples each of soybean meal, hulls, and oil (both crude and refined) processed from these RAC samples.

Conclusions: The submitted soybean processing studies are adequate and indicate that residues of diclosulam do not concentrate in soybean processed commodities. Residues of diclosulam were <0.003 ppm (<LOD) in/on two soybean seed samples harvested 99-127 days after a single at planting preemergence application of diclosulam at 0.09 or 0.25 lb ai/A (~3x or ~8x the proposed rate). Residues were <0.003 ppm (<LOD) in each of two meal, hull, refined oil samples processed from the treated soybean RAC samples. No tolerances for residues of diclosulam in soybean processed commodities are required.

Peanuts

The petitioner submitted data (citation shown below) from two peanut processing studies conducted in GA and TX in 1996.

44315105 McCormick, R.; Bormett, G. (1997) Magnitude of Residues of DE-564 in Processed Products of Peanuts: Lab Project Number:RES96029. Unpublished study prepared by DowElanco. 54 pp

Diclosulam (82.4% DF) was applied to peanuts as a split application consisting of a preemergence treatment applied one day after planting at 0.094 lb ai/A, followed 108 or 131 days later by a postemergence treatment at 0.071 lb ai/A, for a total of 0.165 lb ai/A (~4x the proposed maximum seasonal rate). Samples were harvested 25 or 29 days after the last application.

Peanuts were harvested by mechanical digger and left to dry in the field for 3 or 5 days. One control and treated bulk samples of peanuts (50 lbs each) and one control and two treated RAC samples (3-6 lbs each) were collected from each site and placed in frozen storage within 4 hours of collection. The RAC samples were shipped by overnight carrier on dry ice to DowElanco, Indianapolis, IN, where the samples were kept at ~-20 C prior to analysis. The RAC samples were analyzed within 29 days of collection.

Residues of diclosulam were determined using GC/MSD method GRM 96.01. Adequate concurrent recoveries were obtained from nutmeat (86-99%; $\bar{x}$ = 95±6%; n=6) fortified with diclosulam at 0.01 and 0.1 ppm. Residues were <0.003 ppm (<LOD) in/on two control and four treated samples of peanut nutmeat. As no residues were found in nutmeat samples treated at exaggerated rates, the bulk samples were not processed into peanut fractions.

Conclusions: The submitted peanut processing study is adequate. Residues of diclosulam were below both the LOQ (<0.01 ppm) and LOD (<0.003 ppm) in/on four nutmeat samples harvested ~30 days after split pre- and postemergence applications of diclosulam (84.2%DF) totaling of 0.17 lb ai/A (4.3x the proposed maximum seasonal rate). Peanut processed fractions were not generated. As all peanut nutmeat samples from the RAC field trials and exaggerated rate trials showed residues of diclosulam <0.003 ppm (<LOD), no tolerances for residues of diclosulam in peanut processed commodities are required. The maximum theoretical concentration factor for peanuts is 3x.

OPPTS GLN 860.1480: Meat, Milk, Poultry, Eggs

Ruminant and poultry feeding studies are not required for purposes of establishing tolerances for diclosulam residues in/on peanut nutmeat and soybean seed.

Assuming 0.02 ppm diclosulam residues in/on animal feed items, the calculated maximum theoretical dietary burdens for livestock are 0.02 ppm or less for beef and dairy cattle, poultry, and swine (Table 15). As the petitioner has included an appropriate feeding restriction on the proposed label, peanut and soybean forage and hay have been excluded from the dietary burden calculation (OPPTS.GLN 860.1000, Table 1, footnote 56).

Table 15. Calculation of maximum dietary burdens of livestock animals for diclosulam.

Feed Commodity	% Dry Matter [a]	% Diet [a]	Tolerance (ppm) [b]	Dietary Contribution (ppm) [c]
Beef & Dairy Cattle				
peanut, meal	85	15	0.02	0.0036
soybean, seed	89	15	0.02	0.0032
soybean, meal	92	15	0.02	0.0032
soybean, hulls	90	20	0.02	0.0044
TOTAL BURDEN		65		**0.014**
Poultry				
peanut, meal	NA	25	0.02	0.005
soybean, seed	NA	20	0.02	0.004
soybean, meal	NA	40	0.02	0.008
soybean, hulls	NA	15	0.02	0.0030
TOTAL BURDEN		100		**0.020**
Swine				
peanut, meal	NA	15	0.02	0.003
soybean, seed	NA	25	0.02	0.005
soybean, meal	NA	25	0.02	0.005
TOTAL BURDEN		65		**0.013**

[a] Table 1 (August 1996).
[b] Proposed tolerance. Residues in meal and hulls are based upon the respective proposed tolerances for residues in/on peanut nutmeat or soybean seed.
[c] Contribution = [tolerance / % DM (if cattle)] X % diet).

Based on the calculated maximum theoretical dietary exposure for livestock (0.02 ppm or less for both livestock and poultry), the ~10 ppm dose level used in the ruminant and poultry metabolism studies discussed above reflect ~500-700x dose level. Considering the level of residues found in animal commodities in the metabolism studies at the 10 ppm dosing level, there is no reasonable expectation of finite residues being transferred to animal commodities from the proposed use of diclosulam on peanuts and soybeans; therefore, tolerances for residues in livestock commodities are not required at this time.

OPPTS GLN 860.1850: Confined Accumulation in Rotational Crops

DowElanco has submitted data (citation shown below) depicting the accumulation of ^{14}C-residues in confined rotational crops planted 120 days following a single soil application of [aniline-UL-^{14}C]- or [triazolopyrimidine-7,9-^{14}C]-diclosulam. The in-life phase of the study including determination of total radioactive residues in plants and soil was conducted by Plant Sciences (Watsonville, CA), and the analytical phase was performed by DowElanco (Indianapolis, IN).

> 44103532 Lardie, T.; Stafford, L. (1996) A Confined Rotational Crop Study with (^{14}C)XDE-564 Using Wheat, Lettuce, and Potatoes: Lab Project Number: MET93004: 93.192. Unpublished study prepared by Plant Sciences, Inc. and DowElanco. 140 pp

The test substance, [aniline-^{14}C] or [TP-7,9-^{14}C]diclosulam, having a final specific activity of 40,000 dpm/µg and a radiochemical purity of >99%, was applied once as a spray directly to sandy loam soil (74% sand, 12% silt, 14% clay, and 1.5% organic matter; pH 6.0; and CEC of 13.0 meq/100 g) in containerized, outdoor plots at a rate of 0.05 lb ai/A (1.25x the maximum proposed seasonal rate for peanut crops). On the day after treatment, the control and treated plots were tilled to a depth of 3", and then were left fallow. After the 120-day aging period, the confined plots were relocated to climate-controlled screenhouses and prepared for planting.

Separate treated plots for each rotational crop and ^{14}C-label (six total plots) were planted with wheat, lettuce, and potatoes at a plantback interval (PBI) of 120 days. A total of three separate control plots were also planted with each rotational cropp The wheat and potato crops from treated plots were successfully grown to maturity; however, the treated lettuce plots were replanted at 161 days after treatment due to phytotoxicity, and were replanted again together with Swiss chard at 225 days after treatment. The second replanting of lettuce did not mature past the cotyledon stage, again due to herbicide effects, and the Swiss chard that survived was stunted and did not develop normally. The crops received water, fertilizer, and maintenance pesticides as necessary, and adequate information pertaining to the growing conditions of the crops was provided.

A single sample of each commodity was collected at each PBI from the control and treated plots. Wheat forage was harvested at the boot stage, 56 days after planting (DAP). Surviving Swiss chard was harvested 131 DAP, providing a meager sample. Wheat was harvested at maturity, 112-120 DAP, and separated into grain, chaff, and straw. Potato tubers and desiccated foliage were also harvested at crop maturity, 187 DAP In addition, soil samples (0-6"; 6"-end) were collected before and after application, at each planting interval, and at crop harvest. After collection, plant and soil samples were stored frozen at Plant Sciences 6-14 days prior to shipment on dry ice to DowElanco (Indianapolis, IN).

Crop samples were ground with dry ice and radioassayed in triplicate by LSC following combustion. The specified radioassay LOQs were 0.003 ppm for wheat grain and straw, 0.004

ppm for wheat forage, and 0.002 ppm for potato tubers. The TRRs in/on treated plant commodities are presented in Table 16.

Radioactive residues were generally low (<0.05 ppm) in rotational crop RAC samples with the exception of [TP-7,9-^{14}C]-treated wheat straw from the 120-PBI (0.070 ppm). Radioactive residues were lower in the rotational crops harvested from [aniline-^{14}C]-treated plots than in crops from [TP-7,9-^{14}C]-treated plots. From the [aniline-^{14}C] plots ^{14}C-residues were <0.01 ppm in/on wheat and potato RACs at the 120-day PBI and 0.012 ppm in Swiss chard (225-day PBI). From the [TP-^{14}C] plots ^{14}C-residues were >0.01 ppm in wheat forage, grain, and straw (0.020, 0.025, and 0.070 ppm, respectively) and Swiss chard (0.024 ppm), but 0.008 ppm in potato tubers.

On the day of application, ^{14}C-residues were 0.027-0.042 ppm and 0.032-0.038 ppm in the top 6 inches of soil from the [aniline-^{14}C] and [TP-7,9-^{14}C] plots, respectively. At the 120-, 161-, and 225-day PBIs, ^{14}C-residues in soil were 0.017-0.026 ppm, 0.019 ppm, and 0.017 ppm from the [aniline-^{14}C] plots and 0.023-0.031 ppm, 0.020 ppm, and 0.018 ppm from the [TP-7,9-^{14}C] plots. At harvest, ^{14}C-residues were 0.015-0.023 ppm in the top 6 inches of soil from plots treated with each label.

Table 16. Total radioactive residues found in/on rotational crop matrices grown in a sandy loam soil treated with [aniline-UL-^{14}C] or [triazolopyrimidin-7,9-^{14}C]diclosulam at 0.050 lb ai/A (1.3x the maximum proposed seasonal rate).

Crop	Commodity	Plant-back Interval (days)	Sampling interval [a]		Total Radioactive Residues (ppm) [b]	
			DAT	DAP	[Aniline-^{14}C]	[TP-7,9-^{14}C]
Wheat	forage	120	176	56	<0.004	0.020
	grain		240 [232][c]	120 [112][c]	<0.003	0.025
	chaff		240 [232]	120 [112]	<0.003	0.038
	straw		240 [232]	120 [112]	<0.003	0.070
	straw and chaff		240 [232]	120 [112]	<0.003	0.061
Potato	tuber	120	307	187	0.007	0.008
	mature foliage		307	187	0.011	0.111
Swiss chard	petioles	225	356	131	0.012	0.024

[a] Crop sampling intervals depicted as days after soil treatment (DAT) and days after crop planting (DAP).
[b] Data are expressed in [^{14}C]diclosulam equivalents and are the average of triplicate analyses.
[c] Bracketed values are the sampling intervals for [triazolopyrimidine-7,9-^{14}C]treated plots.

^{14}C-Residues in crop samples were extracted with ACN:H_2O (8:2, v/v), centrifuged, decanted, and concentrated to remove ACN. The ^{14}C-residues were then acidified with HCl (pH <2) and partitioned with EtOAc. Soluble fractions containing radioactivity >0.01 ppm, or sufficient

activity, were analyzed by HPLC. The fractionation and distribution of ^{14}C-residues in rotational crop matrices from the 120-day PBI are presented in Table 17.

As ^{14}C-residues were non-quantifiable in [aniline-^{14}C]wheat grain and straw from the 120-day PBI, these matrices were not extracted. In addition, due to the small sample size and the possibility of contamination with ^{14}C-treated soil, characterization work was not performed on the available 225-day PBI Swiss chard sample.

^{14}C-Residues in the post-extraction solids (PES) of [TP-7,9-^{14}C]wheat grain (43.3%TRR, 0.011 ppm) were extracted with dimethyl sulfoxide (DMSO):water (9:1, v/v) and allowed to stand overnight at room temperature prior to centrifugation. Upon mixing with absolute ethanol (EtOH), a portion of the ^{14}C-residues in the supernatant precipitated as a white solid, characterized by the petitioner as starch, and consisted of 21.3% of the TRR (0.005 ppm). The same extraction procedures performed on control and treated PES yielded similar amounts of starch (3.58 and 3.72 g, respectively). Following DMSO extraction unextracted radioactivity accounted for 9.2% of the TRR (0.002 ppm).

^{14}C-Residues in the PES of [TP-7,9-^{14}C]composite wheat straw/chaff (30.2%TRR, 0.018 ppm), and subsamples were subjected to separate characterization work-ups. Acid hydrolysis of the ^{14}C-residues using 1N HCl at 80 C for 2 hours released 13.3% of the TRR (0.008 ppm); radioactivity in the unextracted solids accounted for 16.7% of the TRR (0.010 ppm). To isolate lignin, a subsample was incubated with chilled (8 C) 72% sulfuric acid for 21 hours, diluted with water and gently boiled for 2 hours. The ^{14}C-residues were cooled, filtered, washed with water until the rinses were at pH ~4, dried, and analyzed by combustion/LSC. A total of 7.8% of the TRR (0.005 ppm) was characterized as lignin in this manner. To isolate cellulose, another subsample was oxidized with combined permanganate solution (CPS, made up of 2 parts of potassium permanganate and one part of buffer: ferric nitrate, silver nitrate, potassium acetate, water, glacial acetic acid, and t-butyl alcohol) for ~2.5 hours, centrifuged, and decanted. The solids were treated with a demineralizing reagent, centrifuged, and decanted. ^{14}C-residues in the remaining pellet were sequentially washed with 80% ethanol and acetone, centrifuged, dried, and analyzed by combustion/LSC. ^{14}C-residues characterized as cellulose from this treatment accounted for 2.3% of the TRR (0.001 ppm). The petitioner stated that similar extraction procedures performed on control post-extraction solids yielded similar amounts of non-radiolabeled lignin and cellulose.

In addition to the analysis of ^{14}C-treated RAC samples, the petitioner also fortified control samples of wheat forage, grain, straw/chaff, and potato tubers with [aniline-^{14}C] and/or [7,9-^{14}C]diclosulam and subjected the fortified samples to the same extraction and fractionation procedures described above. The resulting EtOAc extracts accounted for 95.0-99.5% of the fortified radioactivity. Example HPLC chromatograms of EtOAc fractions from fortified wheat forage and straw/chaff showed only a single peak of radioactivity corresponding to [^{14}C]diclosulam that accounted for ~89% of the initially fortified radioactivity.

Table 17. Fractionation and characterization of ^{14}C-residues in RACs harvested from crops grown in soil treated with [aniline-UL-^{14}C] or [triazolopyrimidine-7,9-^{14}C]diclosulam at 0.050 lb ai/A (1.25x the maximum seasonal rate) at the 120-day plant-back interval.

Fraction	% TRR[a]	ppm	Analysis/characterization
[Aniline-^{14}C]Wheat forage (TRR = 0.003 ppm)[b]			
ACN/H_2O	78.5	0.002	Concentrated, acidified to pH <2, partitioned with EtOAC
Aqueous	24.7	0.001	Not further analyzed
EtOAc	53.8	0.002	
Unextracted	21.5	0.001	
[Triazolopyrimidine-7,9-^{14}C] Wheat forage (TRR = 0.020 ppm)			
ACN/H_2O	87.3	0.017	Concentrated, acidified to pH <2, partitioned with EtOAC
Aqueous	46.1	0.009	HPLC Analysis Unknown peak (R_t=3.0 min) 16.8% TRR; 0.003 ppm Unknown peak (R_t=19.5 min) 9.2% TRR; 0.002 ppm 6 unknown peaks 12.2% TRR; 0.002 ppm each at ≤3.0% TRR (<0.001 ppm)
EtOAc	42.6	0.008	HPLC Analysis Unknown peak (R_t=3.0 min) 10.8% TRR; 0.002 ppm Unknown peak (R_t=23.5 min) 9.7% TRR; 0.002 ppm Unknown peak (R_t=28.0 min) 10.0% TRR; 0.002 ppm 4 unknown peaks 8.7% TRR; 0.002 ppm each at ≤4.3% TRR (≤0.001 ppm)
Unextracted	12.7	0.003	Not further analyzed
[Triazolopyrimidine-7,9-^{14}C] Wheat grain (TRR = 0.025 ppm)			
ACN/H_2O	56.7	0.014	Concentrated, acidified to pH <2, partitioned with EtOAC
Aqueous	41.0	0.010	HPLC Analysis Unknown peak (R_t=2.5-3.0 min) 40.0% TRR; 0.01 ppm
EtOAc	15.7	0.004	Not further analyzed
Solids-1	43.3	0.011	Extracted overnight with DMSO/H_2O (9:1, v/v) at room temperature and centrifuged.
DMSO/H_2O	NR[c]	--	Precipitate with absolute ethanol
Starch	21.3	0.005	
Solids-2	NR	--	Washed with absolute EtOH and centrifuged
EtOH washes	NR	--	Not further analyzed
Unextracted	9.2	0.002	

(Continued; footnotes follow)

Table 17. Continued.

Fraction	% TRR[a]	ppm	Analysis/characterization
[Triazolopyrimidine-7,9-^{14}C] Wheat straw and chaff (composited TRR = 0.061 ppm)			
ACN/H_2O	69.8	0.043	Concentrated, acidified to pH <2, partitioned with EtOAC
Aqueous	39.0	0.024	HPLC Analysis Unknown (R_t=2.5 min) 15.6% TRR; 0.009 ppm 7 unknown peaks 21.8% TRR; 0.013 ppm each at ≤6.3% TRR (≤0.004 ppm)
EtOAc	30.8	0.019	HPLC Analysis 6 unknown peaks 21.8% TRR; 0.013 ppm each at ≤7.1% TRR (≤0.004 ppm)
Solids-1	30.2	0.018	Acid hydrolysis (1N HCl; 80 C, 2 hrs) released 13.3% of the TRR (0.008 ppm). Treatments of separate subsamples with chilled 72% sulfuric acid and combined potassium permanganate solution (CPS) respectively isolated solids characterized as lignin (7.8%TRR) and cellulose (2.3%TRR)
[Aniline-^{14}C]Potato Tubers (TRR = 0.007 ppm)			
ACN/H_2O	55.2	0.004	Concentrated, acidified to pH <2, partitioned with EtOAC
Aqueous	39.1	0.003	Not further analyzed
EtOAc	16.1	0.001	
Unextracted	44.8	0.003	
[Triazolopyrimidine-7,9-^{14}C] Potato Tubers (TRR = 0.008 ppm)			
ACN/H_2O	65.3	0.005	Concentrated, acidified to pH <2, partitioned with EtOAC
Aqueous	55.5	0.004	Not further analyzed
EtOAc	9.7	0.001	
Unextracted	34.7	0.003	

[a] TRR values were corrected for recovery.
[b] Determined by DowElanco.
[c] NR = Not reported.

Radioactive residues in selected solvent extracts and fractions were analyzed by HPLC using a C_{18} column with a gradient of acidified water (0.5% acetic acid) to acidified ACN (0.5% acetic acid). ^{14}C-Residues were detected using an in-line radioactivity detector and by LSC of collected fractions, and unlabeled reference compounds were detected using a UV absorbance detector (250 nm). Reference compounds including parent, ASTP, TPSA, and 5-OH-diclosulam were used for comparison. The characterization of ^{14}C-residues in rotational crops grown in soil

treated with [^{14}C]diclosulam at 0.05 lb ai/A (1.25x) at a plantback interval of 120 days is summarized in Table 18.

The petitioner did not report the sample storage intervals for crop matrices from harvest to TRR determination or to definitive sample analysis; data on the storage of extracts were also not provided (RAB3 estimated sampling to residue analysis took <21 months). These data are required. If plant samples were stored longer than six months from harvest to definitive sample analysis, data demonstrating the storage stability of ^{14}C-residues in rotational crop matrices should accompany the submitted sample storage history. The petitioner should refer to OPPTS.GLN 860.1380(e) for more guidance on the storage stability data required for metabolism studies.

Conclusions: The confined rotational crop study is adequate provided the petitioner furnishes information on the intervals for which samples and sample extracts were held in frozen storage prior to completion of laboratory analyses. If samples were stored longer than six months from harvest to definitive sample analysis, data demonstrating the storage stability of ^{14}C-residues in rotational crop matrices should accompany the submitted sample storage history.

Following a soil application of [aniline-^{14}C] or [TP-7,9-^{14}C]diclosulam at 0.050 lb ai/A (1.25x the maximum seasonal rate), radioactive residues were low (<0.05 ppm) in wheat and potato RAC samples from the 120-day PBI, with the exception of [TP-7,9-^{14}C] wheat straw (0.070 ppm). ^{14}C-Residues in wheat and potato RACs resulting from the application of [aniline-^{14}C]diclosulam were lower (<0.003-0.007 ppm) than ^{14}C-residues resulting from the application of [TP-7,9-^{14}C]diclosulam (0.008-0.070 ppm). For crops harvested from the [TP-7,9-^{14}C] 120-day PBI plots, ^{14}C-residues were 0.008 ppm in potato tubers and 0.020, 0.025, and 0.070 ppm in wheat forage, grain, and straw, respectively. Lettuce crops planted at 120-, 161-, and 225-day PBIs failed due to phytotoxicity; Swiss chard planted at a 225-day PBI had ^{14}C-residues of 0.012-0.024 ppm but was stunted due to phytotoxicity.

Wheat and potato RAC samples containing radioactivity approaching or exceeding 0.01 ppm were adequately characterized by solvent extraction and HPLC analyses. No parent compound was detected. Minor unknown peaks (each at ≤0.009 ppm) were detected in aqueous and organic fractions of wheat forage and straw, along with a polar peak (R_t=3.0 min) from the wheat grain aqueous fraction containing 0.01 ppm. Further characterization efforts were made on post-extraction solids of wheat grain and straw (each ≤43.3%TRR, <0.02 ppm) indicating that ^{14}C-residues were incorporated as natural components (starch, lignin, and cellulose).

Although characterization of ^{14}C-residues in a representative leafy vegetable was not achieved and no attempt was made to obtain samples of a leafy vegetable at PBIs longer than 225 days, no additional data on ^{14}C-residues in a rotated leafy vegetable are required for purposes of this petition as residues of diclosulam are unlikely to occur at detectable levels in rotational crops. Tolerances for rotational crops are not required as long as the label specifies PBIs of 120 days or greater.

Due to the phytotoxicity of diclosulam to suspectable crops, the petitioner is proposing relatively long plantback restrictions for rotated crops: 4 months for small grains, 9 months for cotton, soybeans, and peanuts; 18 months for corn, rice, tobacco, and sorghum; and 30 months for all other crops. RAB3 has no objections to these proposed plantback restrictions. However, the petitioner needs to define "small grains" as wheat, barley, oat and rye.

Table 18. Summary of the characterization of radioactive residues in RACs from rotational crops from the 120-day plant-back interval following an application of [aniline-UL-^{14}C] or [triazolopyrimidine-7,9-^{14}C] diclosulam to the soil at 0.05 lb ai/A (1.25x maximum seasonal rate). [a]

Fraction	Wheat forage (0.003 ppm) *[aniline-^{14}C]*		Wheat forage (0.020 ppm) *[TP-7,9-^{14}C]*		Wheat grain (0.025 ppm) *[TP-7,9-^{14}C]*		Wheat straw/chaff (0.061 ppm) *[TP-7,9-^{14}C]*		Potato tubers (0.007 ppm) *[aniline-^{14}C]*		Potato tubers (0.008 ppm) *[TP-7,9-^{14}C]*	
	%TRR	ppm [b]	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Aqueous	24.7	0.001	46.1	0.009	41.0	0.010	39.0	0.024	39.1	0.003	55.5	0.004
HPLC unknowns [c]	NA [d]		38.2	0.007	40.0	0.010	37.4	0.023	NA		NA	
Organic	53.8	0.002	42.6	0.008	15.7	0.004	30.8	0.019	16.1	0.001	9.7	0.001
HPLC unknowns [e]	NA		39.2	0.008	NA		21.8	0.013	NA		NA	
Post-extraction Solids	21.5	0.001	12.7	0.003	43.3	0.011	30.2	0.018	44.8	0.003	34.7	0.003
1N HCl	-- [f]	--	--	--	--	--	13.3	0.008	--	--	--	--
Starch	--	--	--	--	21.3	0.005	--	--	--	--	--	--
Lignin	--	--	--	--	--	--	7.8	0.005	--	--	--	--
Cellulose	--	--	--	--	--	--	2.3	0.001	--	--	--	--
Total characterized	**100.0**	**0.003**	**90.1**	**0.018**	**77.0**	**0.019**	**82.6**	**0.050**	**100**	**0.007**	**99.9**	**0.008**
Unextracted	NA	--	NA	--	9.2	0.002	6.8	0.004	NA	--	NA	--

[a] Total residues were non-quantifiable in [aniline-^{14}C]wheat grain and straw and were not further characterized.
[b] Expressed in [^{14}C]diclosulam equivalents.
[c] Includes 7-8 HPLC unknown peaks each at ≤0.009 ppm except for [7,9-^{14}C]wheat grain. HPLC analysis of this fraction yielded an early eluting peak (R_t=2.5-3.0 min) at 40%TRR (0.01 ppm).
[d] NA = not applicable
[e] Consists of at least 6-7 unknowns each at ≤ 10.8%TRR (≤0.004 ppm).
[f] -- = Fraction not generated.

OPPTS GLN 860.1900: Field Accumulation in Rotational Crops

Based upon the results of the confined rotational crop study, residues of diclosulam *per se* are unlikely to be detectable in RACs of rotational crops with PBIs of 120 days or greater. Therefore, limited field rotational crop studies are not required for purposes of this petition for the use of diclosulam on soybeans and peanuts.

Other issues

As there are no Canadian, Mexican, and Codex MRLs established for residues of diclosulam in plant or animal commodities, a compatibility problem with U.S. tolerances does not exist at this time.

Attachment 1

Figure A. Chemical names and structures of diclosulam and its metabolites in plants and animals

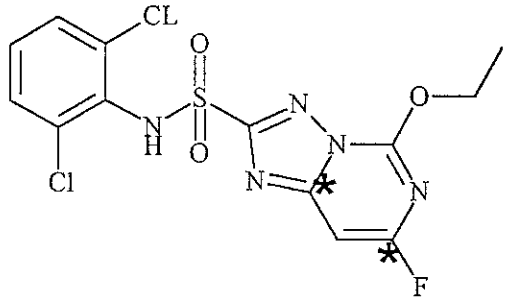
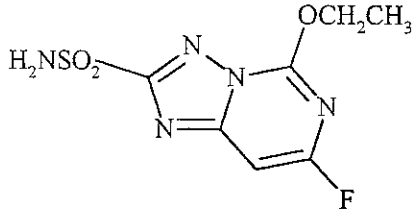
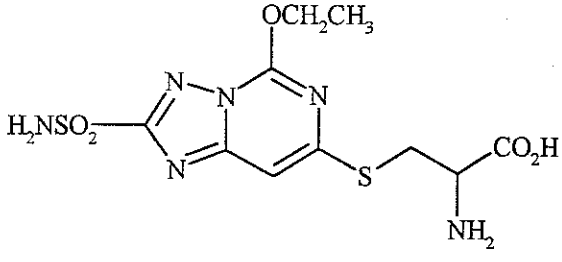
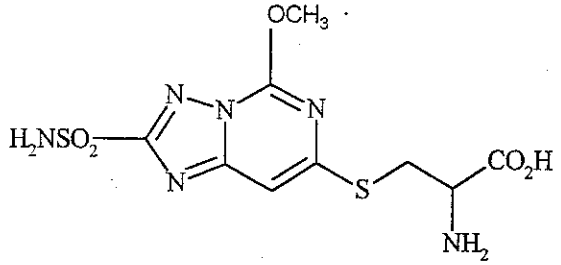
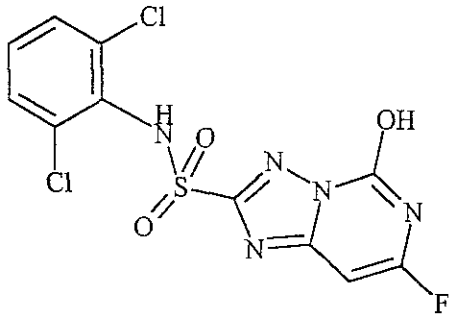
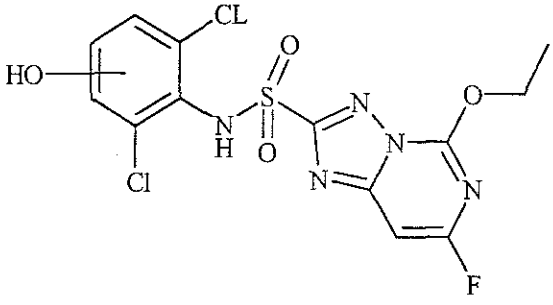
Common Name/Chemical Name	Chemical structure	Matrix
Diclosulam (XDE-564) N-(2,6 dichlorophenyl)-5-ethoxy-7-fluoro-(1,2,4)triazolo[1,5-c] pyrimidine-2-sulfonamide		Hen: liver, muscle, skin, fat, and egg Goat: liver and kidney
ASTP 5-ethoxy-7-fluoro-(1,2,4)triazolo[1,5-c]pyrimidine-2-sulfonamide		Hen: liver, muscle, and egg Goat: kidney
ASTP-Cys (Metabolite C) 7S-[3-aminosulfonyl-5-ethoxy-[1,2,4]triazolo[1,5-c]pyrimidinyl]-cysteine		Soybean: forage
Methyl-ASTP-Cys (Metabolite D) 7S-[3-aminosulfonyl-5-methoxy-[1,2,4]triazolo[1,5-c]pyrimidinyl]-cysteine		Soybean: forage

Figure A. Continued.

Common Name/Chemical Name	Chemical structure	Matrix
5-OH-XDE-564 N-(2,6-dichlorophenyl)-5-hydroxy-7-fluoro-(1,2,4)triazolo [1,5-c]-pyrimidine-2-sulfonamide		Goat: liver
Hydroxyphenyl-diclosulam [a]		Hen: tissue and egg

[a] Tentatively identified by MS analysis. The position of the hydroxyl group is uncertain.

Attachment 9

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

December 6, 1999

MEMORANDUM

SUBJECT: Diclosulam (XDE-564). Outcome of the HED Metabolism Assessment Review Committee (MARC) Meeting Held on 10-26-99 & *Ad Hoc* Meeting Held on December 2, 1999. PC Code 129122. DP Bar Code: D262014

FROM: Leung Cheng, Chemist
Registration Action Branch 3
Health Effects Division (7509C)

THROUGH: Stephen Dapson, Branch Senior Scientist
Registration Action Branch 3
Health Effects Division (7509C)

and

Richard Loranger, Chair
Metabolism Assessment Review Committee
Health Effects Division (7509C)

TO: George Kramer, Executive Secretary
Metabolism Assessment Review Committee
Health Effects Division (7509C)

A. Material Reviewed

The Committee reviewed and discussed the material in the 10-15-99 briefing memo of L. Cheng and G. Dannan including the results of the plant metabolism (peanut and soybean), livestock metabolism (goats and hens), uptake in rotational crops, analytical methodology, magnitude of the residue in peanut and soybean, and animal metabolism (rats) for diclosulam,

also known as N-(2,6-dichlorophenyl)-5-ethoxy-7-fluoro[1,2,4]triazolo[1,5-c]pyrimidine-2-sulfonamide. It was pointed out that the metabolite ASTP on page 8 of the briefing memo should be ASTP-cys, 7S-[3-aminosulfonyl-5-ethoxy[1,2,4]triazolo[1,5-c]pyrimidinyl]cysteine.

B. Conclusions

The Committee concluded that only the parent compound needs to be included in the tolerance expression and used for dietary risk assessment for peanut and soybean. However, since diclosulam contains a 2,6-dichloroaniline (2,6-DCA) group, the Committee also recommended that the registrant provide levels of 2,6-DCA in peanut and soybean at the parts per billion range. The 2,6-DCA data may be derived from either the plant metabolism samples or field trial samples for peanut and soybean. With the proposed feeding restriction of peanut hay and soybean forage and hay, livestock tolerances and feeding studies are not required.

Plant Metabolism (Target crops)

Diclosulam was not detected in peanut nutmeat, peanut forage, mature soybean, and soybean forage. Two metabolites were identified only in the soybean forage, methyl-ASTP-cys and ASTP-cys. These metabolites are assumed to be of comparable toxicity with the parent compound. However, since there will be a feeding restriction of peanut hay and soybean forage and hay to livestock, methyl-ASTP-cys and ASTP-cys need not be regulated in the peanut and soybean crops.

Livestock Metabolism

Diclosulam was present as the major component in the goat and hen. A second compound, 5-hydroxy (or desethyl) diclosulam, was also present in comparable amount in the goat liver. Results of these studies show that finite transfer of diclosulam residues to meat, milk, poultry and eggs is not expected (40CFR§180.6(a)(3) category). The Committee concluded that should feeding studies be necessary in the future, diclosulam should be determined. Furthermore, for dietary exposure assessment in ruminant liver, the level of diclosulam will be doubled to account for 5-hydroxy diclosulam.

Rotational Crops

Many minor metabolites were present and diclosulam was not detected in wheat and potato (activity in sweet chard was not characterized). The Committee concluded that rotational crop tolerances are not required for the time being as long as a plantback interval of 120 days is imposed for all rotational crops. It may revisit this topic when additional 2,6-DCA data in peanut and soybean are available.

Water

Information on the metabolic profile of diclosulam in water was not available at the MARC meeting on 10-26-99. Once this information is available, an *ad hoc* meeting will be held to determine the residues of concern in drinking water.

C. Individuals in Attendance

1. Metabolism Assessment Review Committee
Richard Loranger, Nancy Dodd, William Wassell, Chris Olinger, George Kramer, Kit Farwell, Sanjivani Diwan, Alberto Protzel

2. Metabolism Assessment Review Committee in Absentia
John Doherty

3. Scientists
Leung Cheng (MARC member), Ghazi Dannan

D. Ad hoc Meeting 12-2-1999

An ad hoc meeting was held on 12-2-1999 to discuss the residues of diclosulam in drinking water. Members from EFED (R. Pisigan, R. Parker, A. Chiri) provided the metabolism data of diclosulam in aerobic soil (half-life of parent about 50 days) and estimated concentrations of diclosulam in surface and ground water to HED (MARC members: R. Loranger, G. Kramer, A. Protzel; G. Dannan and L. Cheng). While three metabolites (5-OH-XDE-564, ASTP, and 5-oxo-XDE-564 which is tautomeric with the parent compound) were each present at >10% of the total concentration at some point in time during the aerobic soil study, these compounds in drinking water need not be estimated due to the low toxicity of the parent compound and these metabolites not likely to be more toxic than the parent. Only diclosulam in drinking water needs to be included in risk assessment. The petitioner needs to provide levels of free 2,6-DCA in drinking water in the future.

Attachment: 2 pages of structures

cc:RAB3 Reading F, PP#6F4784 & #7F4856, Cheng, MARC (G. Kramer)

Attachment 1

Figure A. Chemical names and structures of diclosulam and its metabolites in plants and animals

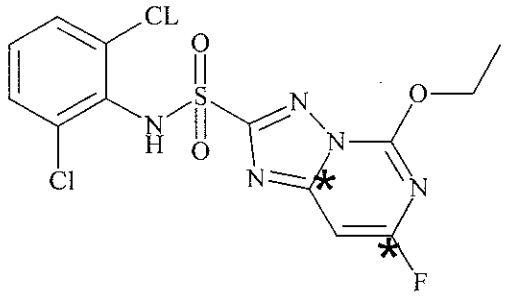
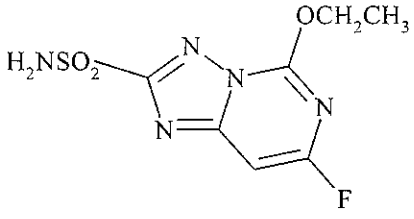
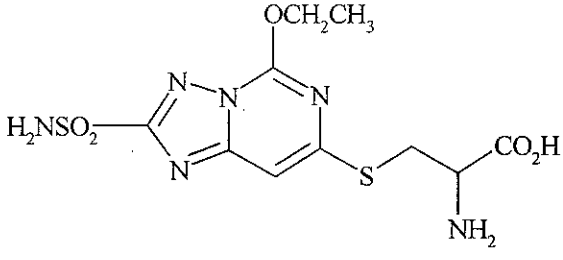
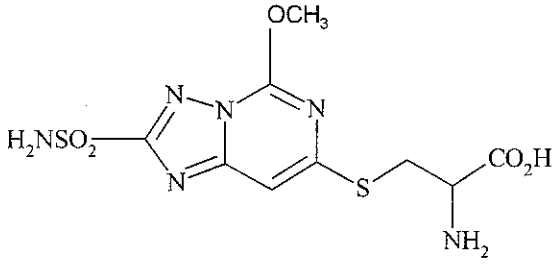
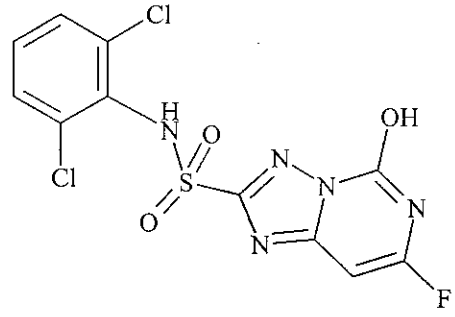
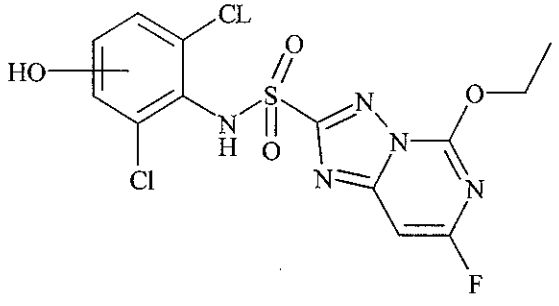
Common Name/Chemical Name	Chemical structure	Matrix
Diclosulam (XDE-564) N-(2,6 dichlorophenyl)-5-ethoxy-7-fluoro-(1,2,4)triazolo[1,5-c] pyrimidine-2-sulfonamide		Hen: liver, muscle, skin, fat, and egg Goat: liver and kidney
ASTP 5-ethoxy-7-fluoro-(1,2,4)triazolo[1,5-c]pyrimidine-2-sulfonamide		Hen: liver, muscle, and egg Goat: kidney
ASTP-Cys (Metabolite C) 7S-[3-aminosulfonyl-5-ethoxy-[1,2,4]triazolo[1,5-c]pyrimidinyl]-cysteine		Soybean: forage

Figure A. Continued.

Common Name/Chemical Name	Chemical structure	Matrix
Methyl-ASTP-Cys (Metabolite D) 7S-[3-aminosulfonyl-5-methoxy-[1,2,4]triazolo[1,5-c]pyrimidinyl]-cysteine		Soybean: forage
5-OH-XDE-564 N-(2,6-dichlorophenyl)-5-hydroxy-7-fluoro-(1,2,4)triazolo [1,5-c]-pyrimidine-2-sulfonamide		Goat: liver
Hydroxyphenyl-diclosulam [a]		Hen: tissue and egg

[a] Tentatively identified by MS analysis. The position of the hydroxyl group is uncertain.

Attachment 10

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: December 6, 1999

Subject: Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration (New Active Ingredient) of Diclosulam on Soybeans and Peanuts

DP Barcode	PC Code	Trade Name:	EPA Reg#	MRID#	PRAT Case	Class	Caswell#	40 CFR
D258377	129122	Strongarm	62719-xxx	N/A	288998	Herbicide		N/A

To: William Wassell, Chemist and Risk Assessor
Registration Action Branch 3
Health Effects Division (7509C)

From: Jack Arthur, Environmental Scientist
Registration Action Branch 3
Health Effects Division (7509C)

Thru: Steven Dapson, Branch Senior Scientist
Registration Action Branch 3
Health Effects Division (7509C)

Introduction

The registrant, Dow AgroSciences, requests the establishment of tolerances for residues of the herbicide, diclosulam on soybeans and peanuts. This memorandum addresses risk from occupational and residential exposure to diclosulam only. An aggregate human risk assessment will be included as a separate HED memorandum.

1.0 Executive Summary

Diclosulam is being considered as a new active ingredient (ai) for herbicidal use. The formulated end use product will be labeled under the trade name, Strongarm. In this memorandum, the name diclosulam will be used for this product.

Only an inhalation toxicity endpoint was chosen for risk assessment. For handlers, daily inhalation exposures were compared to the NOAEL of 10 mg/kg/day from an oral developmental study in rabbits (endpoint: dose-dependent increased abortions, and decreased maternal body weight gain, food consumption, and fecal output) to determine the risk for short-term and intermediate-term inhalation exposures. Results that do not reach a target MOE of 100, present risk concerns. Chronic exposures are not expected for handlers. An occupational postapplication exposure was not conducted. Inhalation, the only route of exposure for which a toxicity endpoint was identified, is not regarded as a significant route of exposure for postapplication activities; especially for a pre-emergent herbicide.

No chemical-specific handler exposure data were submitted in support of this Section 3 registration. It is the policy of the HED to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure Draft Policy # 7, dated 1/28/99).

Handlers who mix and load diclosulam were assessed wearing long pants, long-sleeved shirt, shoes plus socks and gloves, and using the product in water-soluble packets (WSP). Also, handlers who mix and load liquid diclosulam were assessed with the same clothing to cover cases when WSP are premixed before loading into tanks. Handlers who apply diclosulam by groundboom sprayer were assessed in the above clothing (except for the gloves), and using open cab tractors. The MOEs for inhalation, under the above circumstances, range from 250,000 to 1.4 million for handlers. These MOEs are greater than the target (100) and do not exceed HED's level of concern.

The proposed label for diclosulam (i.e., Strongarm) has a 12-hour restricted entry interval (REI). The technical material has a Toxicity Category III for Acute Dermal, with all other acute studies resulting in Toxicity Category IV. Per the Worker Protection Standard(WPS), a 12-hour restricted entry interval (REI) is required for chemicals classified under Toxicity Category III. Therefore, the REI of 12 hours appearing on the Strongarm label is in compliance with the WPS.

There are no residential uses associated with diclosulam.

2.0 Hazard Profile

On October 26, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of diclosulam, and selected the toxicological endpoints for occupational exposure risk assessments (Tables 1 and 2 below).

Table 1. Summary of Toxicology Endpoint Selection.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary		This risk assessment is not required. There is no appropriate study with a single dose and end-point for this risk assessment.	
		Acute RfD = Not Required	
Chronic Dietary	NOEL =5	Decreased body weight gain, changes in renal tubule and kidney function parameters, and increased incidence of male kidney pelvic epithelium hyperplasia.	Chronic Toxicity/ Oncogenicity-Rat
	UF =100	**Chronic RfD =0.05**	
Short- and Intermediate-Term (Dermal)	NOEL≥1000	This risk assessment is not required. In a 21-day rabbit dermal toxicity study, no systemic toxicity was observed at the limit dose (1000 mg/kg/day)	
Long-Term (Dermal)		This risk assessment is not required. Based on the use pattern (1 application/year), there is no potential long-term dermal exposure/risk.	
Short- and Intermediate-Term (Inhalation)	NOEL=10	Increased abortions and decreased maternal body weight gain, food consumption, and fecal output.	Developmental Toxicity-Rabbit
Long-Term (Inhalation)		This risk assessment is not required. Based on the use pattern (1 application/year), there is no potential long-term dermal exposure/risk.	

Table 2. Summary of Acute Toxicity for Technical Diclosulam

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral - Rat	43441021	LD_{50} > 5000 mg/kg	IV
81-2	Acute Dermal - Rabbit	43441022	LD_{50} >2000 mg/kg	III
81-3	Acute Inhalation - Rats	43441023	LC_{50} > 5.04 mg/L	IV
81-4	Primary Eye Irritation - Rabbit	43441024	Slight	IV
81-5	Primary Skin Irritation- Rabbit	43441025	Negative	IV
81-6	Dermal Sensitization - Guinea Pig	43441026	Negative	

3.0 Use Profile

The use profile proposed for this Section 3 registration is summarized in Table 3.

Table 3. Summary of Proposed New Uses for Diclosulam

Product	Use Sites (Pests Controlled)	Application Rate (lb ai/acre)	Number of Applications	Max. Annual Rate (lb ai/A)	PHI (days)
Strongarm (in WSP)	Peanuts (to control broadleaf weeds)	0.024	1	N/A	N/A
	Soybeans (to control broadleaf weeds)	0.032	1	N/A	N/A

4.0 Occupational Exposure

4.1 Handler Exposure and Risk

There is a potential for exposure to diclosulam during mixing, loading, and application activities. An exposure/risk assessment using applicable endpoints selected by the HIARC was performed. Handler's exposure and risk were estimated for the following scenarios: mixing/loading: water-disperable granules in water-soluble packets to support groundboom sprayer; mixing/loading pre-mix liquid to support groundboom sprayer, and; application by groundboom sprayer.

The minimum level of PPE for handlers is based on acute toxicity for the end-use product. The Registration Division (RD) is responsible for ensuring that PPE listed on the label is in compliance with the Worker Protection Standard (WPS).

No chemical-specific handler exposure data were submitted in support of this Section 3 registration. In accordance with HED's Exposure Science Advisory Council (SAC) policy, exposure data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) was used with other HED standard values for acres treated per day, body weight, and the level of personal protective equipment to assess handler exposures. The unit exposure values from PHED are considered to be central tendency. The application rates, treatment variables, etc used in this assessment are upper percentile values. Therefore, the potential dose is characterized as central to high-end.

Exposure assumptions and estimates for occupational handlers are summarized in Table 4.

4.2 Postapplication Exposure and Risk

This Section 3 action on diclosulam primarily involves pre-plant or pre-emergence soil application, with foliage applications limited to certain post-emergence peanut application. Only an inhalation toxicity endpoint was identified. Because potential for postapplication exposure via this route is considered negligible, a risk assessment was not conducted.

The technical material has a Toxicity Category III for Acute Dermal, with other acute toxicity parameters in Category IV. Per the WPS, a 12-hr restricted entry interval(REI) is required for chemicals classified under Toxicity Category III. Therefore, the REI of 12 hours appearing on the diclosulam label is in compliance with the WPS.

Table 4. Exposure and Risk Assessment for Occupational Handlers					
PHED Scenario for Diclosulam Uses	PHED Unit Exposure[1]	Maximum Application Rate (lb ai/acre)	Area Treated (acres/day)	Daily Dose[2] (mg/kg/day)	Short/Intermediate Term Risk (MOE)[3]
(1) Mix/load : Water Dispersible Granules for Groundboom Sprayer (WSP)	Inhalation 0.24 (ug/lb ai) [no respirator]	0.024 Peanuts	80	0.000007	1,400,000
		0.032 Soybeans		0.000009	1,100,000
(2) Mix/load : Liquid for Groundboom Sprayer	Inhalation 1.2 (ug/lb ai) [no respirator]	0.024 Peanuts		0.00003	300,000
		0.032 Soybeans		0.00004	250,000
(3) Application Groundboom Sprayer (Open Cab)	Inhalation 0.74 (ug/lb ai) [no respirator]	0.024 Peanuts		0.00002	500,000
		0.032 Soybeans		0.00003	300,000

[1] Unless otherwise specified, unit exposure values are for workers wearing baseline clothing, (i.e., long-sleeved shirt, long pants, shoes and socks) [no respirator]

[2] Daily Dose =[Application Rate (lb ai/A) x Acres Treated (A/day) x Unit Exposure(ug/lb ai handled) x cf (1 mg/1000 ug)]/Body Weight (70 kg)

[3] MOE = NOAEL/ Daily Dose. Short- and Intermediate-term Inhalation NOAEL=10 mg/kg/day.

5.0 Non-Occupational/Residential Exposure

There are no current registered residential uses for diclosulam.

CC: RAB3 RF, William Wassell (HED), and Jack Arthur (HED)

SignOff Date:	12/ /99
DP Barcode:	D258377
HED DOC Number:	
Toxicology Branch:	RAB3

13544

001002

Chemical:	**N-(2,6-dichlorophenyl)-5-ethoxy-7-fluoro**
PC Code:	**129122**
HED File Code	**14000 Risk Reviews**
Memo Date:	**02/03/2000**
File ID:	**TX014008**
Accession Number:	**412-01-0073**

HED Records Reference Center
12/14/2000